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CLINICAL EVALUATION OF ISOTHIPENDYL HYDROCHLORIDE (THERUHISTIN®)

Report of the Committee on New and Unused Therapeutics

THE Committee on New and Unused Therapeutics of The American College of Allergists was given an initial allotment of a new type of drug that might have usefulness in the control of allergic disorders. After screening this agent (originally designated as Compound AY-56012), members of the Committee felt that it was an effective agent and recommended that the Ayerst Laboratories conduct a full-scale evaluation. Accordingly, the Committee accepted the project; the results of which are presented as a composite report from the cooperating members of the group who have used the drug over a significant period in various parts of the country, thus minimizing the variables of location, climate and seasons.

CHEMISTRY AND PHARMACOLOGY

Theruhistin® is the highly water-soluble hydrochloride of N-dimethyl-amino-isopropyl-thio-pyridylamine whose structural formula appears in Figure 1.[1]

Histamine-induced spasm in the isolated guinea pig intestine was more effectively relieved than other potent available antihistaminic agents. Bronchial spasm produced by aerosolized histamine and acetylcholine were relieved about fifteen times more effectively than compounds of the ethylenediamine and phenothiazine types. Serotonin-induced asthma was blocked also with small dosages. The results were consistent regardless of

Report of the Committee on New and Unused Therapeutics, presented at the Thirteenth Annual Congress of The American College of Allergists, Chicago, Illinois, March 22, 1957.

The Committee on New and Unused Therapeutics include: E. A. Brown, Chairman; S. H. Jaros, co-chairman; P. Blank, E. M. Davis, F. F. Furstenberg, N. H. Gross, E. H. Jones, A. I. Kleinman, S. J. Levin, H. Markow, E. J. Luippold, A. Rowe, J. A. Rudolph, S. Slepian, P. Sperber, W. A. Wright.

the mode of administration of the drug—peroral, subcutaneous injection or by aerosol. The intravenous injection of 0.25 mg/Kg of Theruhistin®, given twenty minutes before, markedly reduced (50-60 per cent) the hypotension produced in the anesthetized cat by the intravenous injection

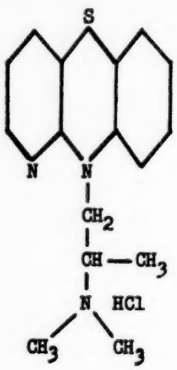

Fig. 1.

of 5 or 10 gamma of histamine hydrochloride. A subcutaneous dose of 10 mg/Kg protected fully 720 mg/Kg of histamine given intracardiacally. A low dose of the drug inhibited also the cardiocirculatory and respiratory depressor effects of serotonin. The drug has a high local vasoconstrictor effect and reduces markedly histamine wheals at low dosage.

In guinea pigs sensitized to eggwhite, the compound protected the animals from aerosolized and injected challenges in the order of about four times better than other potent antihistaminic agents. Like many antihistaminic agents this one shows a local anesthetic effect equal to 40 per cent that of cocaine and to 70 per cent that of xylocaine.

The spasmolytic, neurotropic and musculotropic effect was tested and showed that Theruhistin® has musculospasmolytic effect of 2.8 times that of papaverine and a distinct neurospasmolytic effect of one quarter that of atropine but without any significant mydriatic action. This agent inhibits acetylcholine activity quickly, but lasts only a short time. It serves also as the depressor effect of vagal peripheral and central excitation, except that there is no depression of respiration. The inhibition of secretion of saliva is about one-fiftieth of atropine. It is a weak adrenolytic and the noradrenolytic action is almost nil. In laboratory animals there is no apparent effect on spontaneous locomotor activity or coordination when given in doses of therapeutic range.

Acute and chronic toxicity studies in animals, given doses many times the relative dose that might be used therapeutically in man, showed no specific toxic effects. In human trials, no significant circulatory or central

nervous system effects were seen after large doses were given rectally and intravenously. In sixty patients, who had purposely received three times the average dose for a period of at least a month, a complete hemogram, cephalin flocculation, Bromsulfalein, bilirubin, alkaline phosphatase, thymol turbidity and urine tests were done before and after administration of the drug. In no instance was there any indication of toxicity. One patient, with multiple food allergies, took fifteen 12 mg tablets daily for several weeks without any side effects.

MATERIALS AND METHODS

Placebos and tablets of the drug were distributed to the cooperating members of the Committee who are experienced in the evaluation of such agents. As indicated previously, as many variables as possible were controlled, and those that could not, probably would be minimized by current clinical methods employed in various parts of the country. The drug first was issued in a 2 mg tablet and it soon became apparent that the effective dosage was in a range of 6 to 8 mg. Accordingly, the Company issued a 4 mg tablet with which most of the clinical evidence was obtained.

Each investigator reported separately to the coordinator at the end of the project. No interim reports were issued in order not to prejudice any member. Additional supplies were sent only when requested. The evaluations were collected after a year of trials although the project is not finished since experimental work with other dosage forms of the compound is being done.

RESULTS

The patients' ages ranged from one to sixty-five years, the sexes were almost equally divided, and the duration of therapy was from one week to one year. Table I illustrates the results of the initial trial in 602 instances. It is apparent that the most effective dose is 6 to 8 mg per day with a significant clinical effect of about six hours' duration.

Increasing the dosage to 12 mg per day gave practically 100 per cent effectiveness in the clinical categories tried up to that time. In an extended series, patients taking 12 mg daily for an average period of two months, the results shown in Table II were obtained.

In the initial series of 602 patients only five (0.83 per cent) showed some degree of drowsiness and only one of the forty-four receiving the tablet of 12 mg had this side effect. The total number evaluated is 965 patients to date, with no substantial departure from the results indicated above.

As is usually reported in this type of clinical evaluation there are some patients who fail to respond to any drug; some who prefer another drug because they actually desire the side effects and find them beneficial. For instance, some wish the sedation produced by the ethylenediamines or the

TABLE I. RESULTS WITH COMPOUND AY-56012 (THERUHISTIN®)

	2 mg						4 mg									
	1 qd or 1 prn	1 bid	1 tid	1 qid	1 qd or 1prn	1 bid	1 tid	1 qid	2 qd or prn	2 bid	2 tid	2 qid	3 qd or prn	3 bid	3 tid	3 qid
Urticaria Eczema 0		3	3	4	2	1					1					
1				4		2			1							
2	4	3	2	5		1	1	1			1					
3		7	1	11	4					1	1	1			2	
Total	4	13	6	24	6	4	1	1	1	1	3	1			2	
SE																
Asthma 0	3				1		1	2		1						
1	1	5				3	1	1			1				1	
2		4	10		1	12	7		1		3				1	
3	7	1		9	5	1	6		3		6				4	
Total	11	10	10	9	7	16	15	3	4	1	10				6	
SE	2 drowsy															
Vasomotor Rhinitis 0	1				6				1							
1	2	2		6	2	4					1				1	
2	52	7	6	5	15	4	4		1	1	1				1	
3	1	3		24	28	10	9	2	4	4	6	2			4	
Total	56	12	6	35	51	18	13	2	6	5	8	2			6	
SE			1 drowsy													
Hayfever 0	8			1			7	1			1					
1	17		13				1				4	1				
2	11	4	48		3	2	7				3					
3	14	30	28	1	3	2	1				2					
Total	50	34	89	2	4	16	4	16	1			10	1			
SE	1 drowsy															
Grand total	121	69	111	70	70	42	45	7	11	7	31	4			14	
Per cent Improvement	90.0	95.7	97.3	92.8	88.6	97.6	82.2	57.1	90.9	85.7	93.6	100.0			100.0	

Note: SE denotes side effects.

slight stimulation of other drugs and some patients have learned to use these drugs at certain times of the day depending on their need. Fortunately, the average patient is not such a therapeutist and prefers a compound that will give symptomatic relief without any annoying side effect. This agent is useful in allowing a considerably lowered dosage of a concurrently administered steroid.

DISCUSSION

Current trials indicate that this new type of antihistaminic drug, anticholinergic, antiserotonin agent of the thio-phenyl pyridylamine type gives effective clinical relief in 92 per cent of patients with allergic disease while eliciting an exceedingly low incidence of side effects and no apparent

TABLE II. RELIEF OF PATIENTS USING 12 MG DAILY DOSE OF THERUHISTIN®

	None	Slight	Moderate	Excellent
Urticaria and eczema	2	1		4
Asthma			2	4
Vasomotor rhinitis	7	2	3	3
Hay fever		1		15
Totals	9	4	5	26

toxicity. As is usual with these agents, the best results were obtained in subjects with vasomotor rhinitis and hay fever (up to 96 per cent). It is notable that this compound records better results in bronchial asthma than other compounds probably because it is such an effective antiserotonin and anticholinergic agent as well as being an antihistaminic agent.

Even though the results are not tabulated separately, the compound gave excellent symptomatic relief in patients who had other separate or concomitant allergic manifestations such as gastrointestinal reactions, migraine, iritis, or "id" reactions. In urticaria and eczema, the usual dosage range does not produce the desirable results of other categories; however, when the dosage is increased to about three times the usual, excellent results are obtained. Theruhistin® is exceptionally well tolerated even by infants in doses up to 8 mg at a time. Doses higher than this will produce insomnia in a few rather than sedation.

SUMMARY AND CONCLUSIONS

1. Theruhistin®, a thio-phenyl pyridylamine, represents a new type of antihistaminic drug, anticholinergic and antiserotonin agent which has wide application in the adjuvant therapy of allergic disease and is characterized by a high potency and efficiency with an exceedingly low incidence of side effects.

2. This compound, in the therapeutic range, has been found devoid of any acute or chronic toxicity and is well tolerated by all age groups.

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TREATMENT OF COMMON ALLERGIC DISEASES WITH SUSTAINED RELEASE THERUHISTIN®

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IN A previous communication[1] data were presented indicating the clinical effectiveness of a new antihistaminic, Theruhistin®,* in the treatment of eighty-four patients suffering from various allergic conditions. Because of the negligible instance of side effects associated with its administration, the drug was found to have an outstanding advantage over other equally potent antihistaminics.

A clinical study of Theruhistin® by the Therapeutics Committee of The American College of Allergists[2] revealed it to be extremely effective when used in 602 patients with various allergic disorders, both dermatologic and respiratory. The committee also found the absence of sedation to be striking with drowsiness being observed in less than 1 per cent of the patients.

Brown[3] has classified antihistaminic agents into three groups: Group I —these are the least potent and produce the fewest side effects; Group II—these are moderately potent and cause a moderate number of side reactions; Group III—these are highly potent but also cause the most side effects, particularly sedation.[4] Since Theruhistin,® in this previous communication, was found to be highly potent and remarkably free from sedation and other side effects, a new Group IV can be added to Brown's classification of antihistaminic agents.

Having established the ability of the drug to give adequate relief in allergic conditions with almost no side effects, the present study was undertaken to establish the efficacy of a sustained action Theruhistin® tablet. Green[5] has shown that the incorporation of a clinically effective antihistaminic drug in such a dosage form as a timed sustained release tablet is advantageous, because one of the common faults of antihistaminic drugs, their short duration of action, is thereby overcome. He also observed that sustained action tablets avoided the disadvantage of an immediate high level of antihistaminic activity with sudden drops in activity soon to follow.

Rogers[6] has shown that the administration of chlorprophenpyridamine maleate in a special sustained action capsule, permitting the release of the active ingredient at a slow continuous rate over a period of approximately ten hours, resulted in no reduction of the antihistaminic efficiency of the basic drug. He gives as advantages of this type of administration, "the reduction in side effects, the prevention of predose 'break thru,' the maintenance of an even prolonged optimal level of medication and convenience."

From the Allergy Clinic of Beekman-Downtown Hospital, New York City.
*® Ayerst Laboratories, New York City.

Bancroft,[7] using the same method of administration of the same antihistaminic agent, obtained similar results. He states that "night long protection is necessary for the allergic sufferer and that the regular antihistaminic non-sustained action tablet left many patients unprotected" during this period.

TABLE I. COMPARISON OF ANTIHISTAMIC DRUGS ON GUINEA PIGS

Antihistamine	Number Test Animals	ED_{50} mg/kg	Effective Ratio
Diphenhydramine hydrochloride	20	3.94	1
Isothipendyl hydrochloride (Theruhistin®)	20	0.22	18
Tripelennamine hydrochloride	16	0.33	12
Antazoline hydrochloride	20	5.25	0.7
Chlorprophenpyridamine maleate	20	0.6	7

PHARMACOLOGY OF THERUHISTIN

Von Schlichtegroll[8] studied a large group of thiophenylpyridylamines, synthesized in the course of a search for compounds effective as antihistaminic drugs and without the tendency to produce side effects, particularly sedation. He studied sixty-five such compounds and of all these, Theruhistin® showed the strongest anti-allergic and antihistaminic effect with the least toxicity. He found it extremely effective against histamine-induced spasm of isolated guinea pig intestine and against histamine-induced asthma of the guinea pig when used orally as well as when given by aerosol or subcutaneously.

Its antihistaminic effect is depicted in Table I, where its ED_{50} is compared with other active antihistaminic drugs in Von Schlichtegroll's laboratory experiments. He used diphenhydramine hydrochloride as the standard of one. In this test Theruhistin® surpassed the other antihistaminic drugs tested.

The anti-allergic effect of Theruhistin® was tested by Von Schlichtegroll on guinea pigs first sensitized with three intraperitoneal injections of 1 ml of 20 per cent egg white in physiological saline solution, with a wait of twenty-four hours between each injection. Three weeks after the first injection the animals were exposed for the first time to a spray of the antigens. Within ten minutes the animals reacted with distinct to heavy asthmatic symptoms. If such animals were injected intravenously with Theruhistin® forty-five minutes before the beginning of the test, the protection afforded equalled that seen with tripelennamine hydrochloride and surpassed that seen with chlorprophenpyridamine maleate.

Repeated toxicity studies performed by Von Schlichtegroll with Theruhistin® have not shown any specific toxic effects resulting from its use even when given at many times the therapeutic dose.

MATERIALS

The controlled disintegration tablet of Theruhistin® used in this study contains 12 mg of the active ingredient, isothipendyl hydrochloride. The tablet consists of three layers: outer layer containing 4 mg, middle layer

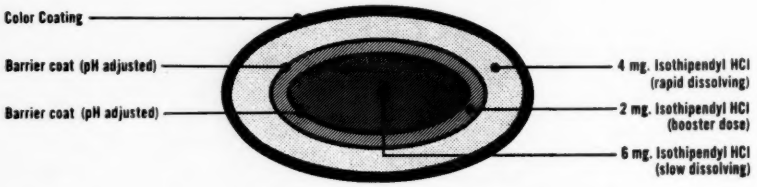

Fig. 1. Diagram showing structure of controlled disintegration tablet of Theruhistin®.

containing 2 mg and the inner core containing 6 mg of the active material. In gastric juice, the outer layer is completely dissolved within fifteen minutes, but the middle layer and the core are unaffected. In intestinal juice, the middle layer is completely dissolved in approximately forty-five minutes. The inner core subsequently disintegrates over a period of three and one-half hours. Thus, the disintegration time for the entire tablet is between four and one-half and five hours.

CLINICAL EVALUATION

The 200 patients treated with sustained action Theruhistin® were taken from private practice and the Allergy Clinic of the Beekman-Downtown Hospital, New York City. These allergic patients represent an unselected group, some of them being treated for the first time, others being chronic cases previously treated with other antihistaminic agents. This study was carried out for a period of twelve months and included the 1957 tree, grass and hay fever seasons.

During the treatment period each patient was seen at least once a week. The acceptability and clinical effectiveness of the sustained action tablet were compared at intervals with the regular Theruhistin® tablet and with other antihistaminic drugs substituted with the patient's knowledge. Comments by the patients and objective findings of the author were recorded. Of the 200 patients treated, 131 received one 12 mg tablet of sustained action Theruhistin® each morning and sixty-nine received one such tablet each morning and each evening.

RESULTS

Two hundred patients were treated with the 12 mg. sustained action Theruhistin® tablet and of these 155, or 77.5 per cent obtained very good results, twenty or 10 per cent had fair results, and twenty-five or 12.5

TABLE II. RESULTS USING ONE 12 MG SUSTAINED ACTION THERUHISTIN®

Diagnosis	Number Patients	Degree of Improvement with One Sustained Action Tablet			Side Effects
		Very Good	Fair	Unsatisfactory	
Tree Fever	25	18	3	4	
Rose fever	17	14	1	2	
Hay fever	23	18	3	2	Headache 1
Allergic rhinitis	27	19	2	6	
Allergic sinusitis	7	3	3	1	
Allergic conjunctivitis	3	3			
Urticaria	15	14		1	
Atopic dermatitis	5	3	1	1	
Contact dermatitis	7	7			Diarrhea 1
Migraine	2	2			
Total	131	101	13	17	2

TABLE III. RESULTS USING TWO 12 MG SUSTAINED ACTION THERUHISTIN®

Diagnosis	Number Patients	Degree of Improvement with Two Sustained Action Tablets			Side Effects
		Very Good	Fair	Unsatisfactory	
Rose fever	13	11	1	1	
Hay fever	24	20	2	2	Drowsiness 1
Allergic rhinitis	14	10	1	3	
Allergic sinusitis	3	2	1		
Urticaria	5	5			Dry throat 1
Angioedema	2	2			
Contact dermatitis	5	4	1		
Poison ivy	1			1	Increase in itching 1
Migraine	2		1	1	
Total	69	54	7	8	3

per cent failed to respond. In over 90 per cent of the patients benefited, the duration of effect of a single 12 mg sustained action Theruhistin® tablet was approximately twelve hours.

SIDE EFFECTS

This study again emphasizes the almost total absence of side effects. Only one patient out of the series of 200 treated complained of drowsiness and in all there were only five side effects reported.

COMMENTS

This study establishes the efficacy of a sustained action tablet of Theruhistin®. The clinical efficacy and low incidence of side effects had already been established for the regular form of the drug. Both have been confirmed again with the use of the sustained release form of the tablet. Thus, further evidence is now available that Theruhistin® falls into a new Group IV classification of antihistaminic agents because of its high potency and low sedative effect.

Granted that the efficacy of the antihistaminic agents now available is in their respective doses relatively equal, Theruhistin® has an outstanding advantage in the negligible instance of side effects associated with its

administration. It is, therefore, highly recommended as an adjunct for relief of symptoms due to allergies to be used along with the well-established therapy of elimination of allergens and hyposensitization.

SUMMARY

Theruhistin® in sustained release form was clinically evaluated in 200 patients in the course of treatment of a number of common allergic diseases. Very good results were obtained in 77.5 per cent of the patients and in all 87.5 per cent were benefited by its administration. In over 90 per cent of the patients benefited, the duration of the effect of a single tablet was approximately twelve hours.

The most outstanding feature of this new antihistaminic agent is its lack of side effects as well as its great potency. In the entire series of 200 patients only one complained of drowsiness.

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Submitted February 27, 1958

ACADEMY OF PSYCHOSOMATIC MEDICINE

The fifth annual meeting of The Academy of Psychosomatic Medicine will be held October 9-11, 1958, at the Park Sheraton Hotel in New York City. The program will be devoted to "The Psychosomatic Aspects of Internal Medicine" and will include formal papers, panel discussions and luncheon conferences. The meeting will be open to all scientific disciplines, as well as psychologists, social workers and nurses. Information may be obtained from Dr. Bertram B. Moss, Suite 1035, 55 East Washington Street, Chicago 2, Illinois.

Physicians in good standing in their county medical society and clinical psychologists with degree of Ph.D. are eligible to join the Academy.

THE BRONCHIAL ASTHMATIC PATIENT AND A NEW THERAPEUTIC MIXTURE*

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THIS study was carried out to determine whether a new therapeutic mixture (referred to as NF-83) containing racephedrine (20 mg), choline theophyllinate (Choledyl®, 200 mg) and pentobarbital (27.5 mg) is effective in controlling chronic asthma and is well tolerated. It was our intention to evaluate this new drug mixture as if it were being used under average office conditions. Therefore, no theophylline blood levels were determined, nor was the patient told that a therapeutic trial was being performed. The "human factor" was taken into consideration at all times, and several courses of treatment with NF-83 were administered at different times and under varying conditions.

This report covers the results in sixty-five unselected cases from a group of over 100 consecutive patients who were treated with NF-83. The remaining cases were not included because they did not go through the complete study.

The sixty-five patients ranged in age from eight to seventy-four years. Twenty-seven were male and thirty-eight were female patients, all having suffered from bronchial asthma for periods ranging from six months to fifty years. With these patients, a medical and allergic history was taken; physical examination, intradermal skin testing, and dietary analysis was performed. Additional studies carried out on many of these patients were: blood counts, urinalysis, sedimentation rates, C-reactive protein, x-rays of the chest and sinuses, electrocardiography, and vital capacity studies.

METHOD OF TREATMENT

Initially, basic therapy consisting of avoidance of offending allergens, hyposensitization, and symptomatic medication was employed in all cases. The new preparation containing choline theophyllinate-racephedrine-pentobarbital (NF-83) was administered to each patient only after the above studies were completed and "avoidance of allergen" therapy had been evaluated.

NF-83 was administered in a fixed dose of one tablet four times a day to all patients. As symptoms changed, dosage was adjusted. The patients were observed for periods ranging from a minimum of three weeks to a maximum of one year. Whenever indicated, additional medication such as potassium iodide, aminophyllin suppositories, epinephrine, or steroid hormones was used in certain patients. However, almost all of the patients

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were treated with the new drug alone, or in combination with potassium iodide. When a patient became asymptomatic, the new drug combination was discontinued, or choline theophyllinate alone was substituted and continued because of its proven prophylactic and therapeutic value.[1-9]

TABLE I. RESULTS USING NF-83 IN TREATING BRONCHIAL ASTHMA

	No. of Patients	Percentage	Associated Conditions*
Good	53	81.5	8
Fair	7	10.8	2
Poor	5	7.7	4

*Thirteen of these patients had emphysema; one patient in the poor group was pregnant.

RESULTS

Each patient acted as his own control and was evaluated on the basis of relief from asthmatic symptoms obtained from the new mixture or in combination with potassium iodide.

Results were described as "good" when relief was complete or almost complete (81.5 per cent); "fair" when relief was only partial in comparison to the patient's condition when initially examined and when compared to the previous course of his disease (10.8 per cent). When little or no symptomatic relief was obtained, we described our results as "poor" (7.7 per cent). Results are shown in Table I.

Many of the patients in whom "good" results were obtained preferred NF-83 to preparations which they had previously used because of the almost complete absence of such side effects as nausea, vomiting, headache, nervousness, excitation, and vertigo. At one point, when it appeared there might be a shortage of NF-83, many patients in the "good" and "fair" groups (including some "fair" patients requiring adjunctive medication) said that they wished to continue their new treatment. This was especially true of the geriatric patients. Symptoms of prostatism arising from vesicle sphincter spasm, which frequently occurs with ephedrine,[10-11] were noticeably absent in the older male patients even with relatively large doses of the new drug. We believe that the absence of this side effect may be due to the presence of racephedrine rather than ephedrine.

A "poor" result was one in which relief from symptoms was not obtained with a dose of two tablets every four hours, administered for at least three weeks for experimental purposes. Several patients reported a few untoward symptoms, such as nervousness and gastric upset. These symptoms disappeared when the dose was again lowered.

SIDE EFFECTS

Our standard initial dosage was one tablet every four hours, on which only one man developed "nervousness, excitement, some nausea, and felt

generally upset." These symptoms disappeared when the dose was reduced to one tablet three times daily. A woman said she felt "sleepy" on the standard dose, but this symptom disappeared when the dose was reduced to one tablet twice daily, and did not recur when she was again placed on standard dosage.

For experimental purposes, and sometimes when therapeutically indicated, we used a dose of two tablets every four hours. On this, five patients reported side effects such as mild vertigo and headache, nervousness and excitation, or nausea. However, these reactions disappeared when the dose was reduced to one tablet every four hours. A woman in this group actually vomited on one occasion but this did not recur.

In attempting to evaluate these side effects, the various components of the new drug were given either singly or in different combinations. Results indicate that it was probably the racephedrine which was responsible for the side effects we have described above.[11] This group also had experienced similar reactions when previously treated with drugs containing theophylline, barbiturate, and ephedrine drugs. Evidently these patients reacted adversely to relatively high doses of these agents. However, NF-83 caused fewer and milder side effects than other forms of medication we had previously used.

DISCUSSION

In evaluating a drug one must be sure that the results obtained are such that they present an accurate representation of the drug's true therapeutic value. The treatment of asthma is difficult because of the clinical variation of the condition itself. Many drugs have been tried which, in first usage, promise effects which are not borne out by continued use.[12-13] For this reason we made a definite effort to treat patients as if they were being handled in "the usual doctor's office" and not under special trial conditions. This is similar to the method described by Brown and Clancy[9] in evaluating one of the components of the present combination (choline theophyllinate). The patients, as a group, were similar to the patients described by these authors.

Perennial and seasonal factors were taken into consideration in this study. The elimination of placebo, blood level studies and other special techniques was decided upon after due consideration of the psychologic implications which these might have in affecting the true picture of the new drug's effects. In addition, since we have observed cases in the past where theophylline levels were high without drug action, we followed these patients long enough to rule out psychologic or placebo effects. Drug fastness did not develop, for symptomatic benefits were in evidence with the same dosage after a year's usage of the drug. Addiction was not apparent.

The onset of action of NF-83 was within hours as compared to choline theophyllinate alone which takes from several days to several weeks or

longer before therapeutic benefits become apparent.[14] This rapid symptomatic action makes the use of this combination ideal for patients who are suffering from active attacks of the disease. The full therapeutic benefits with NF-83 may be expected within one week and the physician must be aware of this fact before expecting maximum symptomatic results in his patients.

We would say that the chronic asthmatic patient having an acute exacerbation of mild or moderate symptoms is the ideal candidate for this new medication. After his symptoms are controlled with the combination, he may then be changed to choline theophyllinate for maintenance or prophylactic therapy. We usually shift our patients to the bronchodilator alone because we do not advocate long-term use of barbiturates, and because some patients may become fast to racephedrine. Usually, the bronchodilatory effects of choline theophyllinate are sufficient to maintain these patients comfortably, so we limit the rapid, powerful action of racephedrine to the control of active asthmatic episodes. This type of therapy must be "tailored" to fit each patient since only with judicious use of the combination may the full benefits be obtained. In addition, prophylactic medication with choline theophyllinate may be employed, without lag periods between attacks, to maintain adequate theophylline blood levels.

SUMMARY

We evaluated, in ambulatory asthmatic patients, a new drug mixture containing racephedrine (20 mg), sodium pentobarbital (27.5 mg), and choline theophyllinate (200 mg), in a series of over 100 patients. These were unselected individuals who had suffered from bronchial asthma for periods ranging from six months to fifty years.

The drug mixture produced satisfactory symptomatic relief in most of the patients and only 7.7 per cent in the series failed to derive any benefits. The main advantage and difference between this and other anti-asthmatic preparations is the relative absence of nervousness, nausea, gastric upset and other side effects that usually result. Another benefit derived is that one of the components of this mixture, choline theophyllinate, may be administered as a prophylactic agent between attacks. This proved to be of particular advantage in the treatment of chronic bronchial asthma.

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THE IMPORTANCE OF CORRECT LANGUAGE

The Rt. Hon. Vincent Massey wrote in *The Listener* (July 18, 1957): "It is commonly observed that our written speech requires correction. We err in two ways. First, we imitate too closely the spoken word, retaining its negligence, its informality, its blunders, while losing . . . colour, [and] vigour of the spoken word. Our second crime is exactly the opposite of our first. When the subject is complex or academic, we throw overboard . . . the strong simple language of speech and . . . [use] the strangest verbal shapes and the most startling figures of speech. . . . An unwary scientist, in a serious statement, can speak with enthusiasm of 'a virgin field pregnant with possibilities.' We are fond of 'ironing out bottlenecks' and 'covering angles.' Metaphorically, however, we are at our best in the international field where the writer of a paper, striving to clarify I know not what, announced to the reader that he now had come to 'the hard core of the third slice of infrastructure'! This may have had something to do with the cold war —it certainly played a part in the cold war against the English language."—(Quoted by *J.A.M.A.*, November 23, 1957).

OBSERVATIONS OF PLASMA AND URINARY STEROID LEVELS FOLLOWING THE ADMINISTRATION OF ZINC-ACTH AND GEL-ACTH

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THE adrenocorticotropic and adrenocortical hormones have become established as useful adjuncts in the therapy of diseases of hypersensitivity. Theoretically, ACTH may be preferable to adrenocortical steroids for use in therapy since it stimulates rather than inhibits the adrenal cortex and produces a more actively functioning rather than an atropic gland. Practically, however, adrenocortical steroids have proved more generally useful in therapy and have been employed much more extensively than ACTH. This is attributable primarily to the fact that no preparation of ACTH satisfactory for oral administration is available.

Since ACTH must of necessity be given parenterally, it would be desirable to have a repository form for this hormone which would prolong maximally the period of effective adrenal stimulation produced by a single injection. Many investigators have attempted to develop such a repository ACTH by adsorbing ACTH on, combining it with, or suspending it in various media. The first such preparation, reported by Wolfson et al,[51] was produced by adsorption of ACTH on colloidal aluminum phosphate. Thereafter, numerous substances were proposed for prolonging the absorption of ACTH. These substances included polyvinylpyrrolidone,[50] gelatin,[34,36,48,49] tannate,[48] various types of oil,[9,36,52] mixtures of oil in beeswax,[3,8] cellulose[33] and procaine.[20]

Further attempts to prolong the action of ACTH were made by incorporating substances which inhibited the enzymatic inactivation of intramuscularly administered ACTH at the injection site. One of the first enzyme inhibiting substances used was polyphorentine phosphate.[18] More recently, zinc (as either phosphate or hydroxide) has been reported to be effective both in inhibiting activity and in delaying the absorption of ACTH.[7,16,21,22,42] It previously was known that zinc salts can potentiate or retard the action of certain protein hormones and inhibit some of the protein-splitting enzymes. Furthermore, it was observed that when zinc phosphate or zinc hydroxide was precipitated from a solution containing

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ACTH about 99 per cent of the ACTH activity was present in the precipitated particles.[22] A suspension of these particles in a simple aqueous vehicle formed a fine, free-flowing, stable preparation which could be injected easily through a small bore needle. Such a suspension of zinc hydroxide and ACTH has been marketed commercially.*

Early investigations of this preparation, which were based on indirect techniques for measuring adrenal function and on clinical studies, indicated that when zinc ACTH was administered intramuscularly it had a more prolonged period of activity than any other available type of repository ACTH.[4,7,11,14,15,16,21,22,26,27,35,42,43,44]

Recently, methods for direct measurement of adrenal hormones which more reliably define the status of adrenal function have become available. Since the desired effects of ACTH are mediated through the production of adrenalcortical hormones, the potency and duration of action of an ACTH preparation is best evaluated by employing these direct techniques. In the present study two repository ACTH preparations, gel-ACTH and zinc-ACTH, have been evaluated. This was done by determining their influence on the plasma 17-hydroxycorticosteroid (17-OHCS) concentrations and the urinary 17-OHCS and 17-Ketosteroid (17-KS) excretions; in addition, the duration of the eosinopenic response produced by each was studied.

METHODS

The ACTH preparations used were for Cortrophin-Zinc®† and Cortrophin-Gel®† obtained from commercially available lots. The subjects consisted of normal young adult men and women. In most instances comparable doses, either forty or eighty units, of each of these repository hormones were administered intramuscularly to the same individual. A waiting period of one month was interposed before the subject was retested with a different dose or preparation. All of these subjects were allowed to maintain normal activity and diet.

Total twenty-four-hour urine samples were collected for one or two days before and for two days following the administration of these preparations. During collection, hydrochloric acid was used as a preservative in the urine, and the urine samples were kept under refrigeration. When the total twenty-four-hour urine volume had been determined, 60 cc aliquots were removed and frozen until analyzed for 17-ketosteroids by the method of Klendshoj, Feldstein, and Sprague,[25] and for 17-hydroxycorticosteroids by the method of Glenn and Nelson.[12]

Heparinized blood specimens were collected between 7 and 8 a.m., just prior to the administration of the ACTH preparation, and then periodically at two to four-hour intervals for a total of twenty-four to thirty-six

*Corticotrophin-Zinc®, Organon, Inc.

†Cortrophin-Zinc® and Cortophin-Gel® were supplied through the courtesy of Dr. K. W. Thompson, Organon, Inc.

TABLE I. 17-OHCS PLASMA LEVEL AND TOTAL EOSINOPHIL RESPONSES TO 40 UNITS ZINC ACTH I.M.

Subject	Age	Sex	Response	Hours Post ACTH						
				0	2	4	8	24	28	32
S.S.	34	M	17-OHCS*	15	50	44	25	7		
			Eosin.**	50	27	5	0	27		
			% Eosin.†	100	54	10	0	54		
J.B.	34	F	17-OHCS	9	22	23	26	0		
			Eosin.	148	148	60	11	55		
			% Eosin.	100	100	40	7	37		
S.B.	28	M	17-OHCS	10	18	22	37	3		
			Eosin.	335	319	165	72	286		
			% Eosin.	100	95	49	21	85		
N.R.	24	M	17-OHCS	7	18	22	31	0		
			Eosin.	71	33	38	5	39		
			% Eosin.	100	47	54	7	55		
H.N.	25	F	17-OHCS	11	23	6	0	18		
			Eosin.	402	286	127	126	110		
			% Eosin.	100	72	32	32	28		
G.W.	29	F	17-OHCS	15	40	19	14	0		
			Eosin.	83	66	22	—	143		
			% Eosin.	100	80	26	—	171		
C.T.	31	M	17-OHCS	14	—	38	40	13	13	8
			Eosin.	110	—	83	0	66	143	66
			% Eosin.	100	—	76	0	60	130	60
J E.	29	M	Eosin.	215	—	138	88	127	165	198
			% Eosin.	100	—	64	41	59	77	92
Average values			17-OHCS	11	28	25	25	6	13	8
			% Eosin.	100	75	44	15	69	104	76

*Micrograms per 100 cc.
**Total number per cu. mm.
†Per cent of the control value.

TABLE II. TOTAL 24 HR. URINARY EXCRETION OF 17-KS AND 17-OHCS PRE AND POST 40 UNITS OF ZINC ACTH I.M.

Subject	Hormone	Total Mgs. Per 24 Hours					
		Control Day		Day Post ACTH			
		—2	—1	1	2	3	4
S.S.	17-OHCS	5.1	6.4	17.1	7.7	10.5	12.6
	17-KS	13.5	10.9	15.5	13.0	14.1	11.6
S.B.	17-OHCS	12.1	4.9	14.1	2.7	2.9	2.8
	17-KS	18.2	19.0	20.6	7.8	18.5	14.4
J.B.	17-OHCS	1.3	1.8	6.7	1.9	1.4	.8
	17-KS	9.1	6.9	8.8	11.3	8.0	5.8
N.R.	17-OHCS	13.2	5.7	30.8	5.3	—	4.7
	17-KS	18.7	18.1	29.2	19.8	—	16.2
H.N.	17-OHCS	1.5	1.3	2.8	1.1	1.1	1.7
	17-KS	3.8	3.6	4.9	3.9	4.8	4.1
C.T.	17-OHCS	1.7	1.4	7.4	1.8	.8	1.0
	17-KS	5.0	1.0	11.6	5.6	3.6	7.7
Average values	17-OHCS	5.8	3.6	13.2	3.4	3.3	3.9
	17-KS	11.4	9.9	15.1	10.2	9.8	10.0

hours. The specimens were centrifuged immediately, and the plasma separated from the cells. The plasma then was frozen until the 17-hydroxycorticosteroids were determined by the method of Nelson and Samuels.[31] The laboratory staff who performed the chemical determinations did not know the dose or the type of ACTH preparation a subject received.

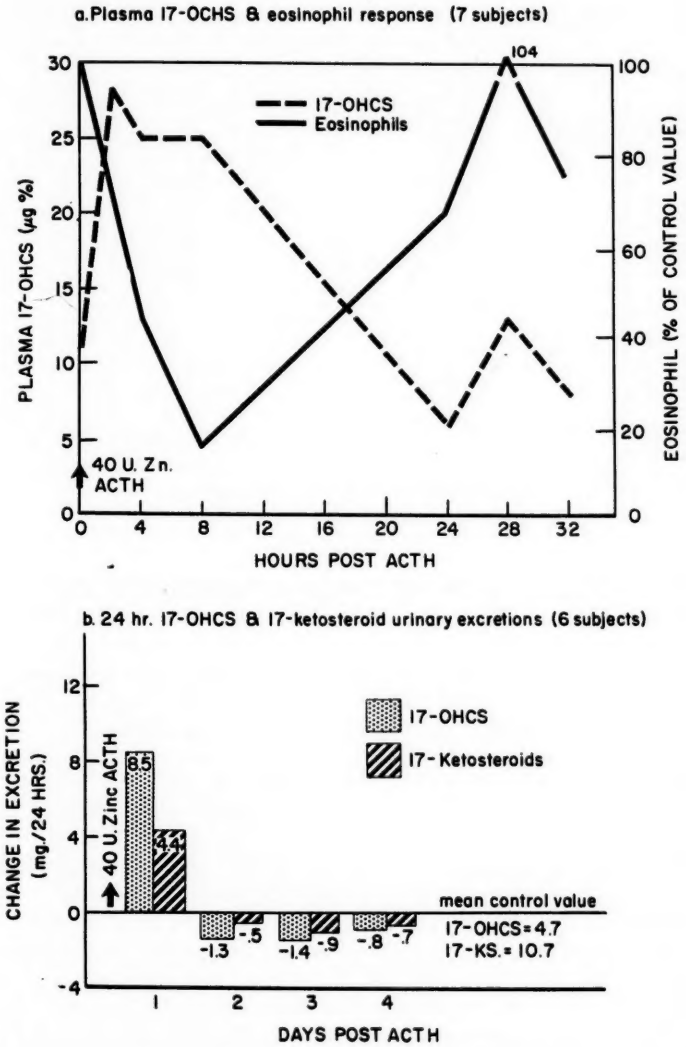

Fig. 1. Response to 40 units Zinc ACTH I.M.

TABLE III. PLASMA 17-OHCS AND EOSINOPHIL RESPONSES TO 80 UNITS OF ZINC ACTH I.M.

Subject	Age	Sex	Response	Hours Post ACTH					
				0	4	8	12	16	24
N.R.	24	M	17-OHCS*	15	29	30	22	24	0
			Eosin.**	880	110	6	11	71	44
			% Eosin.†	100	16	1	2	8	6
R.S.	28	M	17-OHCS	8	8	0	6	10	—
			Eosin.	247	105	17	16	55	—
			% Eosin.	100	43	5	5	22	—
B.B.	32	M	17-OHCS	24	35	50	55	43	—
			Eosin.	187	71	6	11	231	—
			% Eosin.	100	37	3	6	134	—
S.B.	28	M	17-OHCS	—	26	28	31	48	18
			Eosin.	237	127	17	11	11	149
			% Eosin.	100	53	7	5	5	63
G.S.	27	M	17-OHCS	0	31	24	14	—	—
			Eosin.	308	319	11	5	—	—
			% Eosin.	100	103	3	1	—	—
N.R.	24	M	Eosin.	99	71	11	6	28	132
			% Eosin.	100	72	11	6	28	133
Average			17-OHCS	11	26	26	26	31	9
			% Eosin.	100	54	5	4	39	67

*Micrograms per 100 cc.
**Total eosinophils per cu. mm.
†Per cent of control value.

Prior to centrifuging the blood specimens, a total circulating eosinophil count was determined from each of the blood samples by the method of Randolph.[38]

RESULTS

The eosinophil responses obtained in eight subjects following the administration of 40 units of zinc ACTH intramuscularly, and 17-OHCS plasma levels obtained in seven of these subjects are listed in Table I. In Table II are tabulated the twenty-four-hour urinary excretion values for 17-KS and 17-OHCS prior to and following the administration of the zinc ACTH in these same subjects. The results listed in Tables I and II are summarized graphically in Figure 1. It can be observed (Fig. 1) that following the administration of 40 units of zinc ACTH there was a rapid rise in the 17-OHCS blood levels which, in these subjects, persisted for at least eight hours. However, by twenty-four hours the 17-OHCS levels had returned to normal and in the one subject tested remained normal thereafter. It was interesting to note that the eosinopenic response, which has been used by most investigators to determine the duration of activity of this type of ACTH, was still evident at twenty-four hours in spite of the fact that the average 17-OHCS level had returned to within normal limits. The results of the urinary 17-OHCS and 17-KS excretion studies demonstrate quite clearly that following the administration of 40 units of zinc ACTH there was a pronounced increase in the excretion of these

hormones. However, this increased urinary excretion of 17-OHCS and 17-KS was not apparent in the urine samples for any of the subsequent twenty-four-hour periods.

In Table III and Figure 2 are shown responses of plasma 17-OHCS and eosinophils observed following the administration of 80 units of zinc

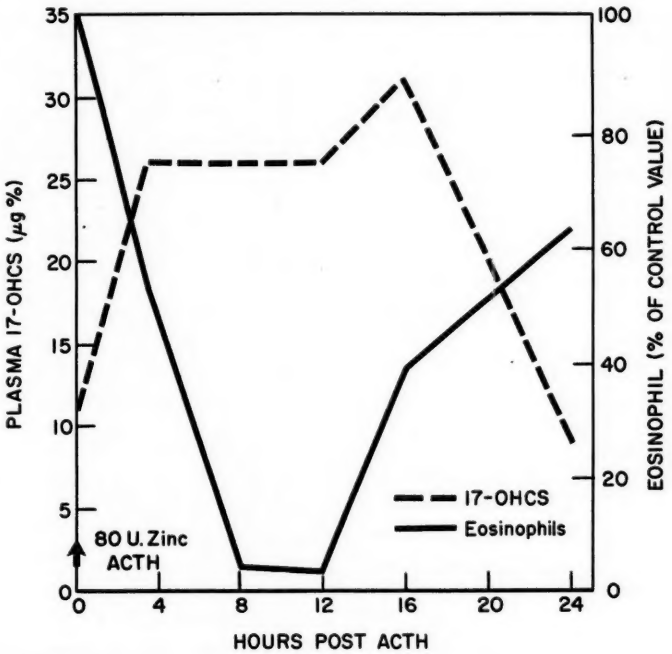

Fig. 2. Plasma 17-OHCS and Eosinophil response to 80 units Zinc ACTH I.M. (Five subjects).

ACTH in five subjects. As noted with 40 units of zinc ACTH, there was a rapid increase in the plasma levels of 17-OHCS. These levels remained elevated for sixteen hours but returned to normal levels by twenty-four hours after the administration of the ACTH. Urinary excretion studies were not performed in these subjects.

The responses of plasma 17-OHCS and eosinophils and of the total twenty-four-hour urinary excretion of 17-OHCS and 17-KS following the administration of 40 and 80 units of gel ACTH are summarized in Tables IV and V and illustrated graphically in Figures 3 and 4. Four hours after the intramuscular administration of either 40 or 80 units of gel ACTH the plasma 17-OHCS were elevated uniformly. The duration of these

TABLE IV. BLOOD AND URINARY CHANGES FOLLOWING 40 UNITS GEL ACTH

Subject	Age	Sex	Blood Changes	Hours Post ACTH						Total 24-Hour Urinary Excretion (Mg./24 Hr.)			
				0	4	8	12	16	24		Control Day	Post ACTH Day 1	Post ACTH Day 2
H.N.	25	F	17-OHCS*	1	—	22	17	0	0				
			Eosin.**	242	50	330	11	22	39	17-OHCS	1.2	12.7	1.4
			% Eosin.†	100	21	136	4	8	16	17-KS	4.7	8.1	4.5
H.S.	32	F	17-OHCS	2	28	25	24	13	0				
			Eosin.	110	16	0	6	0	11	17-OHCS	3.2	13.8	1.6
			% Eosin.	100	14	0	5	0	10	17-KS	15.7	17.2	12.7
S.S.	34	M	17-OHCS	8	25	25	24	10	1				
			Eosin.	489	33	55	11	99	28	17-OHCS	6.9	17.6	5.0
			% Eosin.	100	7	11	2	20	6	17-KS	10.5	15.2	9.5
J. B.	34	F	17-OHCS	0	11	4	0	0	3				
			Eosin.	154	44	55	215	154	248	17-OHCS	.9	8.0	2.2
			% Eosin.	100	28	36	139	100	174	17-KS	7.8	11.3	13.6
Average			17-OHCS	3	21	19	16	6	1	17-OHCS	3.1	13.0	2.6
			% Eosin.	100	18	46	38	32	52	17-KS	9.7	12.9	10.1

*Micrograms per 100 cc plasma.
**Total eosinophils per cu. mm.
†Per cent of control value.

TABLE V. BLOOD AND URINARY CHANGES FOLLOWING 80 UNITS GEL ACTH

Subject	Age	Sex	Blood Changes	Hours Post ACTH						Total 24-Hour Urinary Excretion (Mg./24 Hr.)			
				0	4	8	12	16	24		Control Day	Post ACTH Day 1	Post ACTH Day 2
N.R.	24	M	17-OHCS*	9	21	0	0	0	8				
			Eosin.**	61	17	6	44	61	88	17-OHCS	6.6	29.7	7.3
			% Eosin.†	100	28	10	72	100	144	17-KS	—	27.1	13.2
J.L.	35	M	17-OHCS	8	16	11	17	0	0				
			Eosin.	110	231	60	33	66	435	17-OHCS	4.3	23.5	3.7
			% Eosin.	100	210	54	30	60	395	17-KS	16.6	31.2	18.3
			17-OHCS	5	31	16	—	1	6				
S.B.	28	M	Eosin.	545	148	22	77	357	154	17-OHCS	3.1	8.2	3.1
			% Eosin.	100	27	4	14	65	28	17-KS	8.8	13.0	11.8
Average			17-OHCS	7	23	9	8	0	5	17-OHCS	4.7	20.5	4.7
			% Eosin.	100	88	23	39	75	189	17-KS	12.7	23.8	14.4

*Micrograms per 100 cc plasma.
**Total eosinophils per cu. mm.
†Per cent of control value.

elevated levels varied considerably among individual subjects; however, by sixteen hours all had returned to normal.

The pattern of eosinopenia after 40 units gel ACTH was approximately the same as that after 40 units zinc ACTH. However, the eosinopenia following 80 units of zinc ACTH was of longer duration than that following

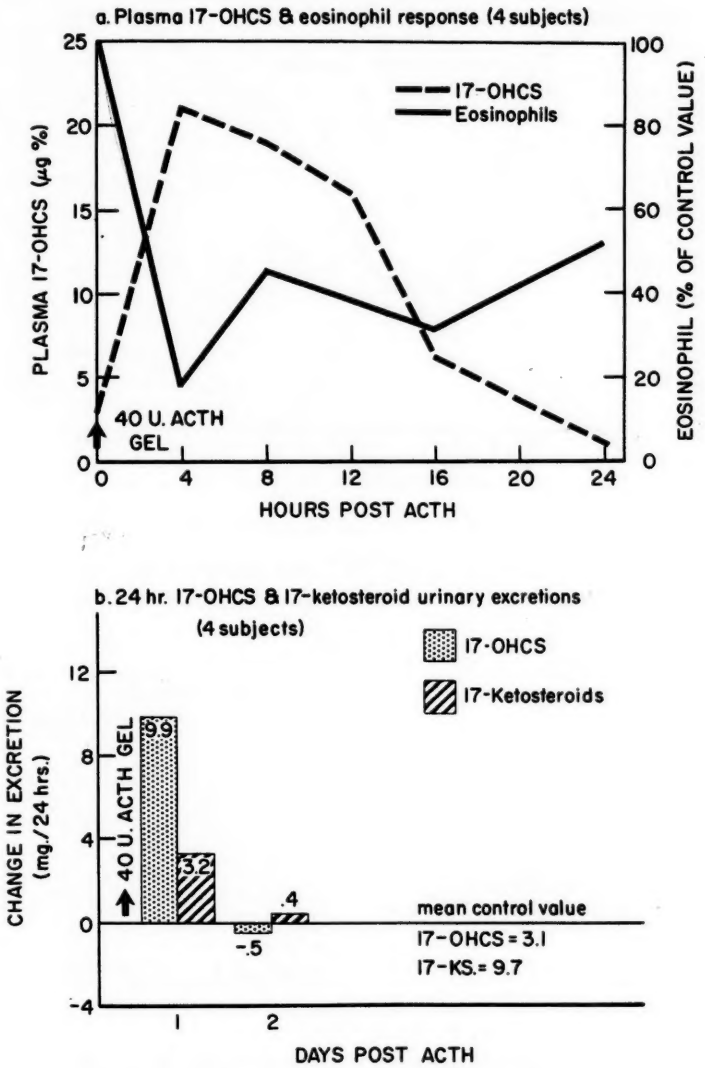

Fig. 3. Response to 40 units Gel ACTH I.M.

*Micrograms per 100 cc plasma.
**Total eosinophils per cu. mm.
†Per cent of control value.

80 units of gel ACTH. Again, as with zinc ACTH, the urinary 17-OHCS and 17-KS excretions during the first twenty-four-hour period following 40 or 80 units of gel ACTH were markedly increased. However, as indicated in Figures 3 and 4, elevated urinary excretion values for these hormones were not observed in subsequent twenty-four-hour periods.

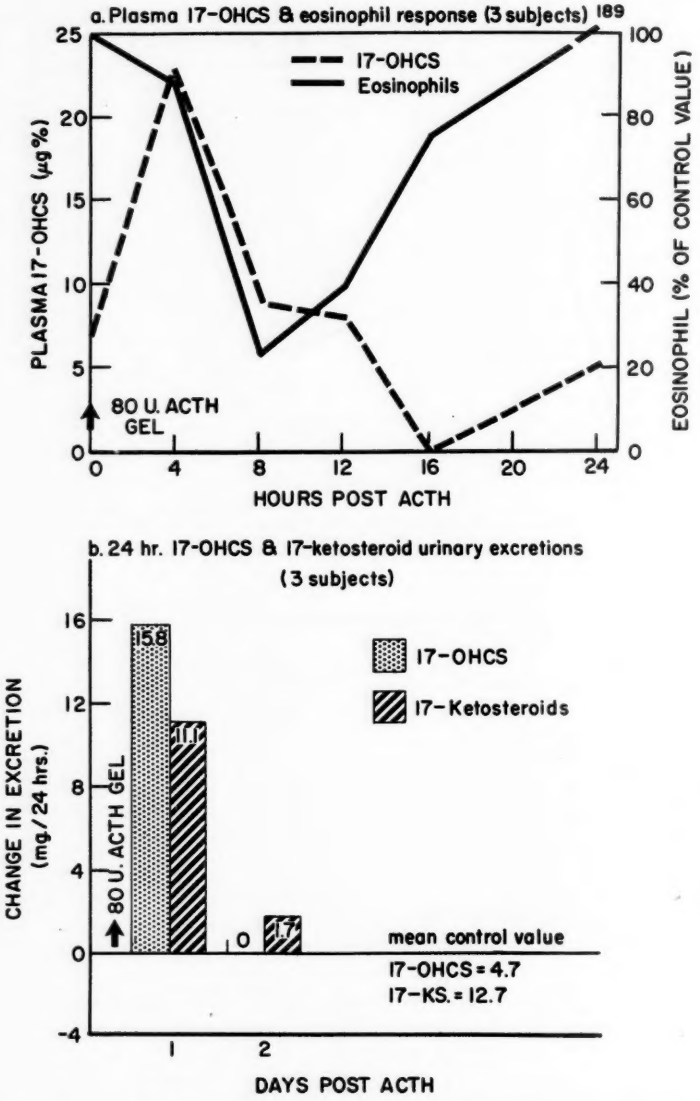

Fig. 4. Response to 80 units Gel ACTH I.M.

As was true following zinc ACTH, following gel ACTH the change in 17-OHCS excretion was much more marked than was that in 17-KS excretion.

Figure 5 compares graphically the responses of plasma 17-OHCS following zinc ACTH and following gel ACTH. It is apparent from these

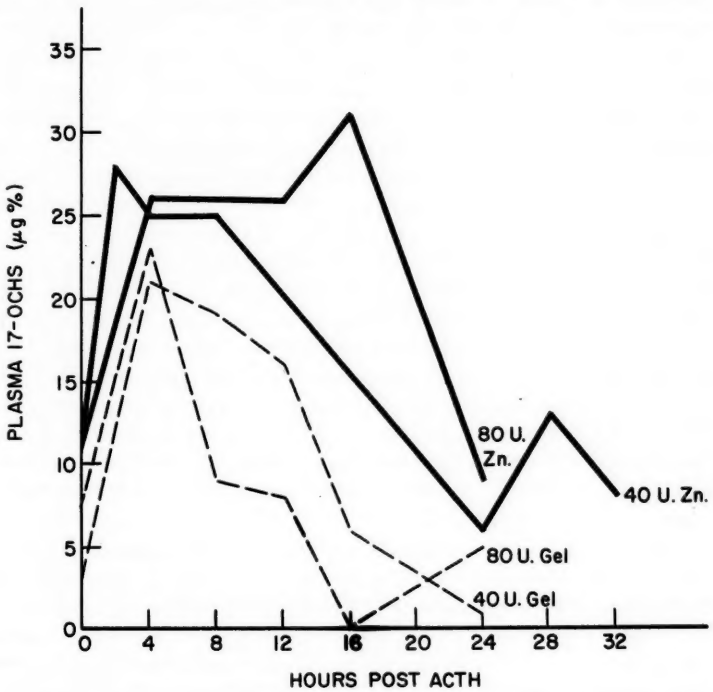

Fig. 5. Comparison of Plasma 17-OHCS response to Zinc ACTH and Gel ACTH I.M.

data that 40 units of either ACTH preparation elicit essentially the same response as did 80 units. It also is apparent that zinc ACTH exerted a more prolonged stimulating effect than did gel ACTH.

Despite these differences in response of plasma 17-OHCS concentrations, the urinary excretion values for 17-KS and 17-OHCS were essentially the same following 40 units of either zinc or gel ACTH. However, the steroid excretion values following 80 units of gel ACTH were considerably greater than those following 40 units.

DISCUSSION

The adrenal cortex responds to stimulation by even minute amounts of endogenous ACTH. In normal man, the circulating concentrations of en-

dogenous ACTH ordinarily are not detectable by the most sensitive blood ACTH assays yet devised;[32,45] this has been interpreted as indicating an ACTH concentration of less than 0.5 milliunits per 100 ml of blood. Similar concentrations have been found in normal dogs and cats.[41] Even in severely stressed animals[29] and human subjects,[17] who exhibit clear evidence of adrenal activation, the concentrations of endogenous ACTH are not greater than a few milliunits per 100 ml of blood.

Similarly, minute amounts of exogenous ACTH, if administered intravenously, will induce adrenal activation. Thus, in the hypophysectomized rat 0.25 milliunit of ACTH almost invariably induces a significant depletion of adrenal ascorbic acid.[41] In the hypophysectomized dog[30] 2.5 milliunits of ACTH produces a significant increase in steroid concentration in adrenal vein blood. In the intact guinea pig[28] as little as 0.01 unit of ACTH is reflected by increased urinary excretion of adrenocortical steroids. In man, Bayliss and Steinbeck[1] demonstrated maximal stimulation of the adrenal cortex by administering one unit of lyophilized ACTH intravenously per hour; Eik-Nes[6] et al reported a maximal adrenal response with 25 units of lyophilized ACTH administered intravenously over a six-hour period; Bliss et al[2] using rapid intravenous injection of ACTH found 15 units of lyophilized ACTH to produce a maximal response; and Renold et al[39] have presented data suggesting that a concentration of 3 milliunits per 100 ml of plasma induces a definite response and a concentration of 12 milliunits per 100 ml of plasma induces a maximal adrenal response.

Based on the observation that the adrenal cortex responds to minute doses of ACTH, Gordon[13] advised the use of continuous intravenous administration. The half-life of ACTH in the circulation is extremely short;* and the duration of adrenal stimulation resulting from a single rapid injection of ACTH is brief.[2] Intravenous infusion of ACTH over a long period of time produces a much greater adrenal response than rapid intravenous injection of a comparable dose.[40] Although continuous intravenous administration is conceded to be the most effective means of giving ACTH (as judged by the response induced per unit of ACTH), the technical difficulties incumbent upon its use constitute obvious disadvantages. Furthermore, when the intravenous route is used, there is a greater risk of a severe systemic allergic reaction to the ACTH.

Because of the difficulties attendant upon intravenous administration of ACTH, it generally has been administered intramuscularly. However, when administered intramuscularly ACTH is rapidly inactivated by tissue. Hamburger[18,19] has reported that ninety-five to ninety-eight per cent of intramuscularly injected ACTH is inactivated in the tissues and that only relatively small amounts of active ACTH are absorbed. Because of this and because of the brief half-life of ACTH after entering the circulation,

*Reported to be approximately one minute in the adrenalectomized rat.[46]

the duration of adrenal stimulation induced by intramuscular injection of ACTH is brief;[37] hence there is a real need for continuously potent, long-acting preparations of ACTH.

Although the number of subjects in the studies reported here was relatively small, the results of the data presented indicate quite clearly that zinc ACTH is a potent repository ACTH preparation. Furthermore, when the plasma 17-OHCS responses to zinc ACTH and gel ACTH are compared there is evidence suggestive that unit per unit zinc ACTH has a longer period of activity than gel ACTH. This is particularly evident when the 17-OHCS responses to 80 units of zinc ACTH and of gel ACTH are compared (Fig. 5). This difference in effect on plasma 17-OHCS concentrations induced by the two ACTH preparations is not reflected by the urinary excretion data.

Although it appears that zinc ACTH has a longer period of activity than gel ACTH, its duration of activity did not exceed twenty-four hours in the subjects studied. This was clearly demonstrated by the return to normal of 17-OHCS plasma concentrations within twenty-four hours after the administration of zinc ACTH. The observation of normal steroid excretion values for the second twenty-four-hour period following administration lends further support to this interpretation. The plasma 17-OHCS responses confirm Kassenaar's[23] findings and are in agreement with Geller and co-authors,[10] who unbeknown to the present authors had simultaneously conducted a similar type of study. Studies of the urinary excretion of hormones were not performed by the above investigators.

These interpretations are in contrast to those of other investigators who concluded from the eosinophil responses and clinical studies that the duration of activity of zinc ACTH was from twenty-four to seventy-two hours. Several factors may account for this discrepancy. First, eosinopenic responses to the administration of ACTH do not necessarily reflect the magnitude of adrenocortical response.[6,24] Therefore, the assumption that the eosinopenia following zinc ACTH reflects continuing increased release of adrenocortical hormones may be incorrect. The present studies tend to support this contention. Thus, as is shown in Figure 1 and Figure 2, an eosinopenic response was still evident twenty-four hours after administration of zinc ACTH in spite of the fact that the average 17-OHCS plasma level had returned to normal. Secondly, the clinical response of a patient to ACTH is extremely difficult to evaluate and, therefore, probably a poor index for accurately determining the duration of activity of an ACTH preparation. Since the present study has demonstrated that zinc ACTH is an excellent preparation which has a longer period of activity than gel ACTH, it is not surprising that after its administration patients experience good clinical results. Furthermore, it is not uncommon for patients who have had adequate suppressive doses of ACTH or steroids to be asymptomatic for twelve to forty-eight hours following discontinuation of the hormones.[47] Thus, it is conceivable that this asymptomatic period may

have been interpreted as evidence of prolonged ACTH action. Thirdly, it is conceivable that repeated injections of zinc ACTH could produce a cumulative effect and that due to incomplete absorption or destruction in the muscle tissues the duration of its activity might be lengthened. In the present study the duration of activity was investigated only following single injections of either ACTH preparation. And, finally, discrepancies in duration of activity may occur among different ACTH lots because of errors in the original assays for potency or due to variable loss of activity with varying length or type of storage of the preparation. No evidence of loss of potency in over a year's time was observed in the preparations investigated.

Considering the evidence that a sustained adrenal response is elicited by these repository ACTH preparations, particularly by zinc ACTH, one might expect to find a definite dose-response pattern. This was not seen for plasma 17-OHCS elevations when the 40 and 80 unit doses of ACTH were compared. Actually, in the small groups studied the magnitude and duration of plasma 17-OHCS elevations in response to 40 units of either ACTH preparation were comparable to those to 80 units. These findings are in keeping with the observations of Bayliss and Steinbeck[1] and Eik-Nes,[5] mentioned previously who found maximal adrenal response to occur following the intravenous administration of relatively small doses of ACTH. The plasma levels of 17-OHCS following the maximal stimulation by intravenous ACTH found by these two investigative groups are comparable to the 17-OHCS levels observed in the present study after intramuscular administration of 40 units of ACTH. This would make it appear likely that a single intramuscular injection of 40 units of either zinc ACTH or gel ACTH produces a nearly maximal elevation of plasma 17-OHCS concentrations. However, the data concerning urinary steroid excretions did show some dose-response relationship; the excretions following 80 units of gel ACTH were definitely greater than those following 40 units. It is not clear whether this finding indicates a degree of adrenal response beyond that detected by the plasma steroid levels, or whether it reflects an altered excretion pattern.

SUMMARY AND CONCLUSIONS

Zinc ACTH and gel ACTH were administered intramuscularly in normal subjects to determine their potency and duration of activity. The method employed consisted of directly measuring the circulating plasma 17-OHCS levels, the total twenty-four-hour urinary excretion concentrations of 17-OHCS and 17 ketosteroids, and determining the eosinopenic response following the administration of these preparations.

The results of these studies indicate that zinc ACTH is longer acting than gel ACTH. The duration of activity of zinc ACTH, as determined by the plasma 17-OHCS response, persists from eight to sixteen hours, but is less than twenty-four hours. That the duration of activity of zinc

ACTH is not more than twenty-four hours was further suggested by the return to normal after twenty-four hours of the urinary 17-KS and 17-OHCS excretion values.

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The authors wish to express their appreciation for technical assistance to Hideko Nakamura, Jean Burnett, and Betty Reid.

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Submitted December 9, 1957

COMBINED MEETING
WEST VIRGINIA STATE SOCIETY OF ALLERGY WITH THE WEST VIRGINIA ACADEMY OF OPHTHALMOLOGY AND OTOLARNGOLOGY

The West Virginia State Society of Allergy and the West Virginia Academy of Ophthalmology and Otolaryngology will have a combined meeting on Thursday, August 21, 1958, at 2:00 P.M. during the section meetings of the West Virginia State Medical Association, The Greenbrier, White Sulphur Springs, West Virginia.

The West Virginia State Society of Allergy will act as the host group for this combined meeting. The program will consist of speakers and a seminar on allergy problems in relation to practice. There will be three outstanding speakers who will participate in this meeting. These are Dr. Leon Unger, who will discuss allergy of the eye, ear, nose and throat with emphasis on nasal polypi, Dr. J. Warrick Thomas who will discuss the relationship of allergy to general practice with emphasis on allergy to insects. The third speaker will be Dr. Philip Blank, who will discuss the practical aspects of pediatric allergy as seen by the ophthalmologist, the otolaryngologist, the pediatrician, and the general practitioner. In addition to the speakers there will be a panel discussion conducted by the speakers with audience participation. The moderator for this program will be Dr. Merle S. Scherr, Charleston, West Virginia, who is President of the West Virginia State Society of Allergy.

The program will be practical and will be opened to all physicians attending the West Virginia State Medical Association Meeting.

DERMAL CONTACT DERMATITIS FROM NEOMYCIN
Observations On Forty Cases

STEPHAN EPSTEIN, M.D., F.A.C.A.
Marshfield, Wisconsin

DURING the last two years I have observed over forty cases of proven contact sensitivity to neomycin. Yet contact dermatitis from neomycin generally is considered rare, and apparently often goes unrecognized. As neomycin is a valuable drug, and a widely used topical antibiotic, attention should be called to the particular form of dermal sensitivity which neomycin may produce.

The following are particular aspects of contact dermatitis from neomycin:

1. The clinical appearance, in many instances, is that of an aggravation or "irritation" of a pre-existing dermatitis, and not the obvious picture of an acute contact dermatitis. The original dermatitis most often is an infectious eczema of the ear. Only after several weeks or months does the neomycin dermatitis spread to other areas, usually to the eyelids first.

2. The use of preparations containing both neomycin and hydrocortisone, such as Neo-Cortef®,* Hydroderm®,* and Cortisporin®,* at times appears temporarily helpful in spite of existing sensitivity to neomycin.

3. Patch tests with neomycin-containing preparations and even a 10 per cent neomycin solution, are negative, in the majority of cases. In those instances where positive patch tests are obtained, they are at times only inconstantly positive. The reaction consists of a papular eruption, not of vesicular lesions.

4. Intradermal tests with a 1:1,000 dilution of neomycin are usually positive, and those with a 1:100 dilution apparently are always positive. The reaction occurs as delayed, tuberculin-type papules which appear after twenty-four to forty-eight hours and persist for one to several weeks; at times they are accompanied by a flare-up of the original lesions.

REPORT OF FORTY CASES

There were fourteen males and twenty-six females, varying in age from seven to eighty-two years. Tables I and II give the location and diagnosis of the original lesions, respectively.

Presented at the 13th Annual Congress of The American College of Allergists, March 22, 1957, Chicago, Illinois.

From the Department of Dermatology, Marshfield Clinic, Marshfield, Wisconsin, and the Division of Dermatology, University of Minnesota Medical School, Minneapolis, Minnesota.

*Neo-Cortef®, a product of The Upjohn Company, contains neomycin and hydrocortisone; Hydroderm®, a product of Merck, Sharp & Dohme, neomycin, bacitracin and hydrocortisone; and Cortisporin®, a product of Burroughs Wellcome & Company, neomycin, polymyxin B, bacitracin and hydrocortisone.

TABLE I. LOCATION OF ORIGINAL LESIONS

Ears	15
Other parts of face	10
Arms, hands, legs, feet	8
Anogenital area	3
Other locations	4

TABLE II. DIAGNOSIS OF ORIGINAL LESIONS

Infectious (bacterial) eczema, or infection	17
Contact dermatitis	11
Atopic dermatitis	6
Eczema of eyelids	3
Seborrheic dermatitis	2
Miscellaneous	1

The sensitizing preparations were identified in thirty-four of the forty cases; in the remaining six, there was a strong suspicion that neomycin-containing medications had been applied. These were mostly ointments, creams and lotions, but included eye drops and ear drops. In seventeen instances, preparations containing both neomycin and hydrocortisone had been used.

The following case reports are representative:

Case 6.—This patient shows proven sensitivity to neomycin in spite of negative patch tests.

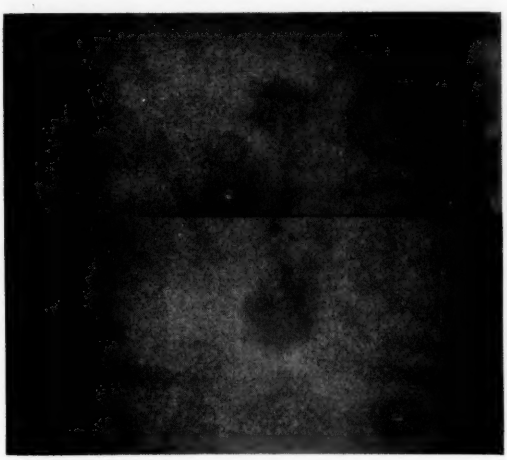

Fig. 1. Positive intradermal tests to neomycin. Above is the forty-eight-hour reaction to 0.05 cc of a 1:1,000, below to a 1:100 solution of neomycin. (Case 6.) For biopsy of the 1:100 test, see text and figure 8.)

A man, twenty-nine years of age, was seen because of a resistant infectious dermatitis around his nose. The patient had used neomycin and penicillin ointments without results. A patch test with neomycin was negative, and 2.5 per cent Neo-Cortef®

ointment was prescribed. About two weeks later his condition became aggravated and his ears involved. There were alternating periods of improvement and aggravation. Six months later the patient was again seen, and neomycin sensitivity was suspected.

Repeated patch tests with Myciguent®, Neosporin® and Neo-Cortef® ointments were negative except for one out of three patch tests with Neosporin® ointment which after seventy-two hours showed a minor follicular eruption covering an area of 5 x 9 mm.

Intradermal tests with neomycin were strongly positive (Fig. 1).

Case 15 presents dermal contact dermatitis from neomycin, superimposed on an infectious plus atopic dermatitis of the ears.

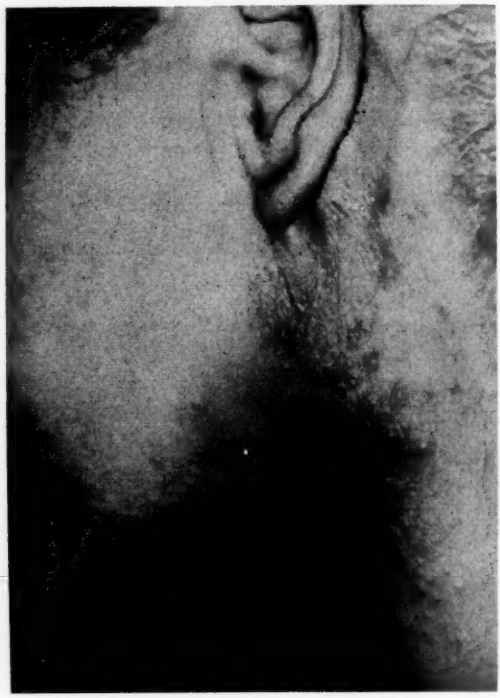

Fig. 2. "Aggravation" of eczema of ears by neomycin-containing preparations. (Case 15.)

A woman, fifty-seven years of age, suffered from an eczema of her ears for two years. Neo-Cortef® ointment seemed to give relief, but later was followed by aggravation (Fig. 2). Patch tests with several neomycin-containing ointments were nega-

Neo-Cortef® is a product of The Upjohn Company.
Myciguent® is a product of The Upjohn Company.
Neosporin® is a product of Burroughs Wellcome and Company.

tive, but intradermal test reactions were strongly positive. Elimination of neomycin-containing preparations was followed by improvement. Whenever the patient, against medical advice, used these preparations again, there was a definite flare-up. However, discontinuation of neomycin-containing ointments and ear drops alone brought only partial and temporary relief, because neomycin sensitivity was only one part of the picture.

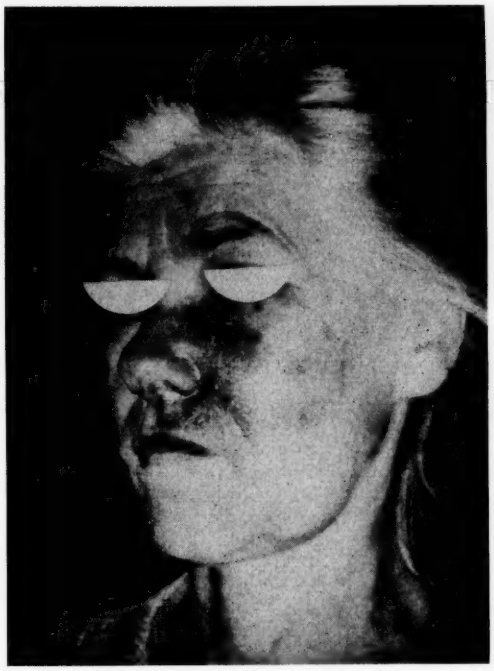

Fig. 3. Contact dermatitis following application of a neomycin-containing ointment to a treated basal cell epithelioma. (Case 16.)

Contrasting is the next case where elimination of a neomycin-containing ointment cleared up a troublesome eczema of the ears and eyes, which had lasted for about two years. In this instance, apparently, sensitivity to neomycin alone was responsible for the persistence of the eczema.

Case 28.—A white woman, forty-two years of age, suffered from an eczema of her ears for two years, which spread to her eyelids. During the past year she had used an ointment containing neomycin and hydrocortisone. Her eczema did not clear up, but spread to the neck. When first seen, neomycin sensitivity was suspected; patch tests with neomycin-containing ointments and a 10 per cent neomycin solution were negative; but intradermal tests were strongly positive; the 1:100 dilution producing a delayed reaction measuring 28 mm in diameter, and persisting for over seven weeks.

Case 33 presents an aggravation of pruritus ani by neomycin sensitivity.

The patient, a white man, seventy-six years old, had been successfully treated in 1954, with Neo-Cortef® for pruritus ani. Two years later when he used the same ointment to treat a recurrence of his pruritus ani, he noticed an aggravation of the condition. Here again, patch tests with neomycin were negative, but intradermal tests were positive. The pruritus ani and its aggravation cleared up under bland treatment, after avoidance of neomycin-containing ointments.

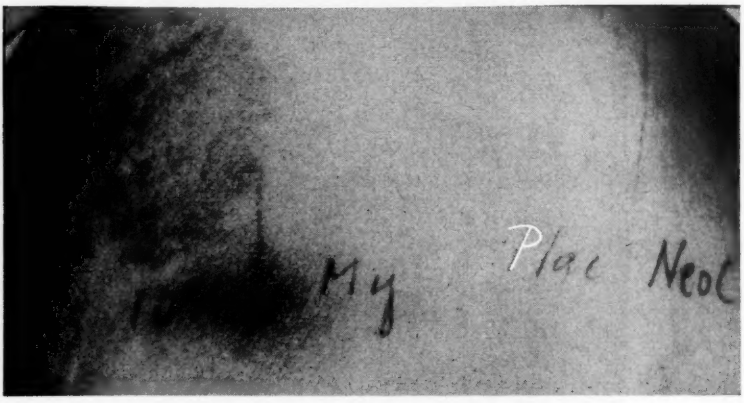

Fig. 4. Positive patch test with a 10% neomycin solution after twenty-four hours. (Case 16.) Note papular type of eruption. (For biopsy see Fig. 5.) Patch tests with Myciguent (My), and Neo-Cortef (NeoC) were negative after twenty-four hours, but produced a mild papular reaction after forty-eight to seventy-two hours.

Neomycin can also produce the typical picture of a contact dermatitis, as seen in the following case:

Case 16.—A white woman, fifty-eight years of age, received Myciguent® ointment in 1954 after treatment of a basal cell epithelioma on her face. Within a few weeks a contact dermatitis developed on her left cheek around the wound (Fig. 3). Later on, it spread to neck, chest and arms. Patch tests carried out in 1954, after the dermatitis had healed, gave a positive reaction to Myciguent® ointment containing 0.5 per cent neomycin, and to a 5 per cent solution of neomycin. Repetition of the patch tests two years later produced a papular dermatitis at the site of the test with 10 per cent neomycin within twenty-four hours (Fig. 4, left); patch test reactions to 0.5 per cent neomycin-containing ointments were negative after twenty-four hours, but turned positive after forty-eight to seventy-two hours, demonstrating persistence of the sensitivity for over two years. Intradermal tests with neomycin were strongly positive.

DIAGNOSIS OF NEOMYCIN SENSITIVITY

A clinical diagnosis of neomycin sensitivity is made when neomycin-containing preparations cause an aggravation of a pre-existing dermatosis and when the removal of such preparations leads to an improvement or disappearance of the dermatitis. The specific sensitivity is proven by

TABLE III. DERMAL CONTACT DERMATITIS FROM NEOMYCIN
Results of skin tests

Patch Tests	Intradermal Tests
5% or 10% Neomycin Solution and/or Neomycin-Containing Preparations.	1:1000 and/or 1:100 Solution.
Positive 9	35 .....Positive
Negative 26	0 .....Negative
Total 35	35 .....Total

skin tests. However, as Table III shows, patch tests with neomycin-containing ointments and/or 10 per cent solution of this drug are positive in only about one-fourth of the cases; therefore, one has to depend on the result of intradermal tests which apparently are positive in all cases (Table III), when carried out with the proper concentration.

Both patch and intradermal test results should be observed for at least three days, because the reactions may not show up at all, or not very strongly during the first forty-eight hours.

Positive intradermal tests are considered proof of allergic dermal hypersensitivity to neomycin because controls on over thirty-five test persons not clinically sensitive to neomycin were always negative, with one exception. This patient, with a history of a previous skin eruption due to penicillin and aureomycin sensitivity, reacted with an itching papule to the 1:100 dilution of neomycin.

Of course, when interpreting delayed intradermal reactions, one must be careful not to consider as positive, a transient traumatic reaction due to the injury from the injecting needle. These latter reactions are usually less than 5 mm in diameter and disappear or fade after twenty-four to forty-eight hours, whereas the allergic response increases in size and intensity after forty-eight hours. I have not had any difficulty in distinguishing these traumatic "needle reactions" from the allergic test reaction. However, in a few (five) cases of suspected neomycin sensitivity, I have observed equivocal reactions to the 1:100 dilution of neomycin, which may or may not have been on an allergic basis; for the purpose of this study these instances were eliminated.

A note of caution about the intradermal tests is indicated; the positive test often turns into a patch of eczema which may persist for many weeks. Sidi, Hincky and Longueville,[5,15] and I, also have observed flare-ups of the original dermatitis following positive intradermal tests.

HISTOPATHOLOGY OF SKIN TESTS WITH NEOMYCIN

Skin tests with neomycin were examined microscopically.*

Patch tests were studied after twenty-four hours (Case 16, Fig. 4, left), after ninety-six hours (Case 6), and after nine days (Case 40).

*I am indebted to Dr. Hermann Pinkus for sectioning and interpreting the biopsies and for furnishing the photomicrographs.

Biopsy after twenty-four hours (patch test with 10 per cent neomycin): "The sections (Fig. 5) show an inflammatory infiltrate in the upper corium, centering mainly around the uppermost portion of the sweat duct and around the one hair follicle present. The periductal epidermis is spongiotic and invaded by mononuclear cells."

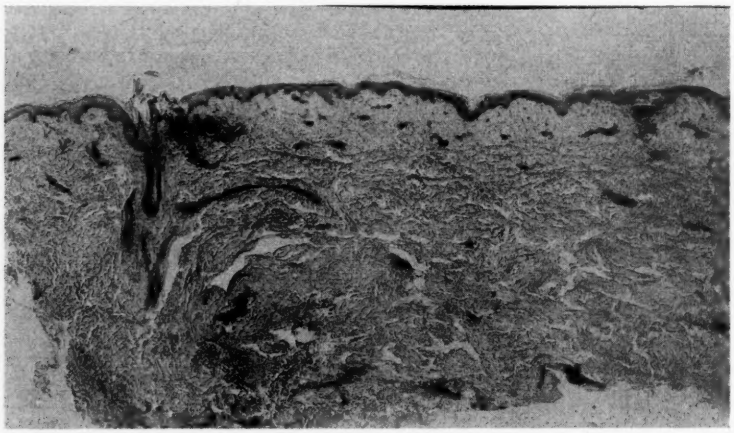

Fig. 5. Biopsy after twenty-four hours of patch test with 10% neomycin. (Case 16, Fig. 4.) The main characteristic is an infiltrate of the upper dermis; epidermal changes (spongiosis only in the periductal epidermis, around the openings of follicles and sweat glands).

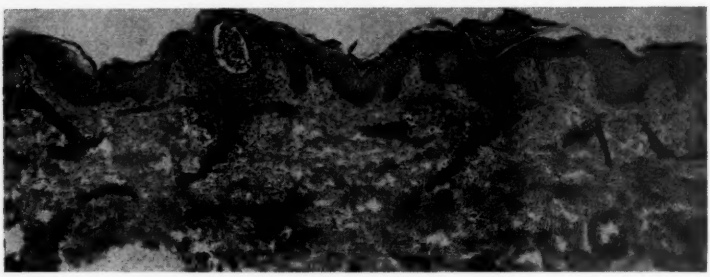

Fig. 6. Biopsy, after ninety-six hours, of patch test with Neosporin® ointment. (Case 6.) Thickening of epidermis and intraepidermal vesicles associated with sweat pores. Perivascular infiltrate in the upper dermis.

Biopsy after ninety-six hours (patch test with Neosporin® ointment—Fig. 6): "The epidermis is slightly thickened and shows well-circumscribed intra-epidermal vesicles, some of which are already being cast off as parakeratotic crusts. All these individual lesions are associated with sweat pores, but appear to be paraductal, the duct finding its way around the vesicle or spongiotic zone. The vesicles seem to originate by spongiosis and are filled with desquamating prickle cells. There is moderate perivascular infiltrate in the upper corium associated with these vesicles."

Biopsy after nine days (patch test with 10 per cent neomycin solution): "There are a few small areas of intra-epidermal edema and a tiny vesicle, but no acanthosis. The upper corium shows a monocytic infiltrate."

In summary, the patch tests to neomycin showed mainly a monocytic infiltrate in the upper and middle corium, and only moderate epidermal changes, mostly paraductal.

Intradermal tests.—Positive intradermal tests with a 1:100 solution of neomycin were biopsied after forty-eight hours (Case 6), after six days (Case 1), after nine days (Case 40), and after thirty-one days (Case 38). These are the findings:

After forty-eight hours (Fig. 7).—"There is much perivascular round cell infiltrate in the corium, no eosinophils are seen. The epidermis shows edema only around sweat ducts, otherwise seems unaffected."

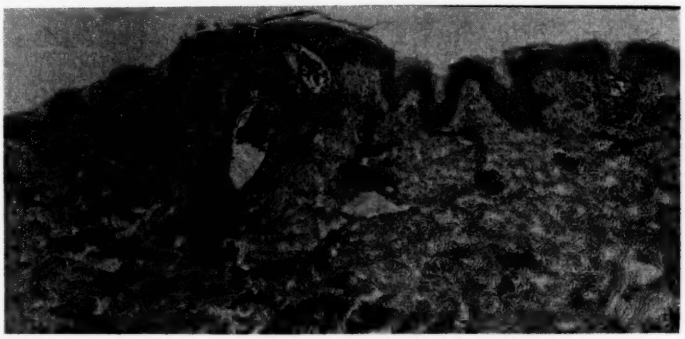

Fig. 7. Biopsy, after forty-eight hours, of intradermal test with a 1:100 solution of Neomycin. (Case 6, Fig. 1). Perivascular round cell infiltrate in the dermis; the epidermis shows edema only around sweat ducts. (See text.)

After six days (Fig. 8).—(This patient also had a seborrheic dermatitis.) "The sections show real eczematous dermatitis with a suggestion of the seborrheic type. There is moderate acanthosis with spotty spongiosis and at least one good intra-epidermal spongiotic vesicle. These changes are accompanied by spotty parakeratosis and small parakeratotic crusts resembling the mound-like crusts of seborrheic dermatitis. There is considerable exocytosis of leukocytes into the epidermis. The corium contains a moderate perivascular infiltrate, mostly lymphocytes with some neutrophilic and an occasional eosinophilic leukocyte."

It is interesting that an intradermal test on apparently normal skin of a seborrheic individual produced a reaction which resembled seborrheic dermatitis.

After nine days.—"The sections show a more pronounced cellular infiltrate in the upper and middle corium and very little epidermal changes."

After thirty-one days.—"There is a heavy, and in places almost granulomatous, infiltrate in the corium. The epidermis shows some acanthosis and edema and invasion of leukocytes, resembling eczematous dermatitis."

In summary, the intradermal tests showed a more marked infiltrate of the corium, and the epidermal changes, at least in the earlier stages, were largely confined to the periductal epithelium. In general, there was a considerable similarity of the histologic picture of patch and intradermal

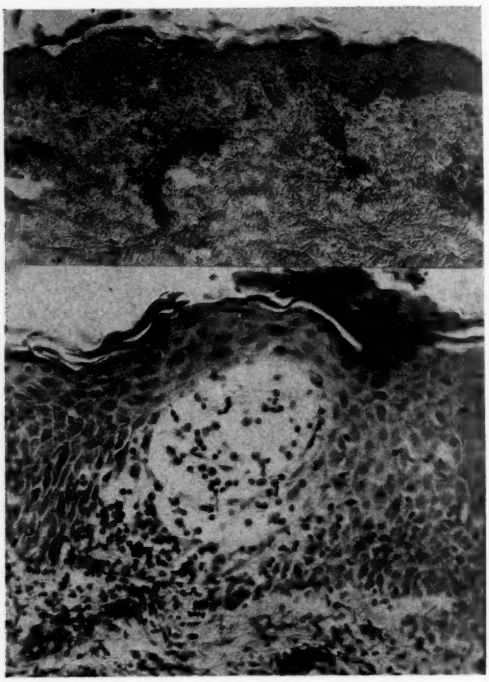

Fig. 8. Biopsy after six days, of intradermal test with 1:100 solution of neomycin, in a patient who also suffered from a seborrheic dermatitis. (Case 1.)

test characterized by a preponderance of the infiltrate in the corium, and relatively minor epidermal changes, which became more pronounced as time went on.

DISCUSSION

The purpose of this presentation is not just to add another sensitizer to the growing list of offenders, but mainly to discuss a peculiar form of contact dermatitis.

FREQUENCY OF SENSITIZATION TO NEOMYCIN

Allergic sensitivity to neomycin generally has been, and still is, considered rare. Kile, Welsh and McAfee,[1] in 1950 first reported on the use of neomycin-containing ointments; in over 200 patients no case of irrita-

tion had been proved to be due to neomycin. In a further communication, Kile, Rockwell and Schwarz[2] state that in a total of 869 cases there was only one instance of definite sensitivity to neomycin. However, they add that in a group of nine patients showing irritation, there may have been more than one person who was sensitive to neomycin, but this was not substantiated by patch test reactions. This observation seems significant in view of my findings of negative patch tests with neomycin in the presence of positive intradermal tests. Livingood and his co-workers[3] had treated 264 patients with topical neomycin without a single instance of allergic sensitivity. Baer and Ludwig[4] reporting a case of contact dermatitis from neomycin in 1952, considered its sensitizing index remarkably low. This still is the opinion of Sidi, Hincky and Longueville[5] (1956), and Appel[6] (1957). But, apparently, sensitivity to neomycin was observed more often than recognized, e.g. by Sloane,[7] who considered four instances due to an "irritation" as contrasted to hypersensitivity. It seems reasonable to assume that this "irritation" represented dermal sensitivity with negative patch tests. Pillsbury[8] feels quite sure that a number of instances of neomycin sensitivity are passed off on the basis of mild irritation, because there has been so much confidence that the compound rarely produces sensitization.

Since I published my preliminary reports[9,10] on dermal sensitivity to neomycin, Neils Hjorth[11] from Copenhagen reported twenty-three cases of neomycin sensitivity, and two instances with only positive intradermal tests.*

SIGNIFICANCE OF NEOMYCIN SENSITIVITY

Neomycin is a valuable drug; it is one of the most potent topical antibiotics, it does not stain, and so far it is used relatively little internally; therefore, sensitization to neomycin usually does not carry as great a risk as sensitivity to an antibiotic widely used systemically, such as penicillin.

But there is a real danger. Neomycin has become the most widely used topical antibiotic. There are, in the U.S.A. alone, over fifty topical preparations such as ointments, creams, lotions, eye drops, nose drops, and sprays and ear drops containing neomycin.† Because of the erroneous impression that it rarely produces sensitization, a deplorable habit has developed to use neomycin in combination with something else, when an antibacterial agent is really not needed at all. I, too, have labored for a long time under this illusion, and used neomycin routinely as a prophylactic without strict indication (Case 16).

*While this paper was in print, James F. Hildebrand, Sheboygan, Wisconsin, kindly informed me that during a period of 2½ years, he observed 15 cases of neomycin sensitivity (personal communication).

†Neomycin may also cause allergic conjunctivitis, with or without accompanying dermatitis of the eyelids.

Apparently the cosmetic industry has taken a similar stand. Since Shelly and Cahn[12] described the deodorizing effect of neomycin, deodorants, soaps and other cosmetics now contain neomycin (Ippen,[13,14] Pillsbury[8]). These preparations may become new sources for sensitization, or may become a hidden cause of a dermatitis in a neomycin-sensitive person.

Neomycin sensitivity assumes an added importance in view of the fact that in France this drug is now more widely used systemically for tuberculosis, and also since Sidi and Hincky[15] reported cross-sensitivity between neomycin and streptomycin.

USE OF TOPICAL NEOMYCIN

Experience on thousands of cases has proved the efficacy of topical neomycin. Compared to its value, the risk of sensitization is not great enough to discourage its use where it is indicated. In cases of neomycin sensitivity, I use other antibiotics or antiseptics, either alone or in combination with hydrocortisone, such as Terra-Cortril®*, Vioform Hydrocortisone® cream, or an ointment of equal parts of Ilotycin®* ointment and 1 per cent Cort-Dome®* cream.

DERMAL AND EPIDERMAL SENSITIVITY IN CONTACT DERMATITIS

In contact dermatitis either the epidermis or the dermis may become sensitized, or both. Therefore we have—at least theoretically—two forms of contact dermatitis: one where the epidermis is the main shock organ ("epidermitis"), and the other where the dermis is the chief organ of reaction (dermitis"). The reason is probably this: In contact dermatitis the allergen is a so-called simple chemical which by itself is not a complete antigen. In order to become one it has to combine with some of the body's proteins. It seems likely that some of these chemicals combine only, or mainly, with proteins of the epidermis; then we have epidermal contact dermatis, manifested clinically by a vesicular dermatis and microscopically by spongiosis and intraepidermal vesicles. Other chemicals apparently attack proteins of the dermis, and then the complete antigen is formed in the dermis, and dermal contact dermatitis results, manifested clinically by a papular dermatitis and microscopically by a dermal infiltrate. Some, perhaps most, chemicals probably attack proteins both from the epidermis and dermis, and then a mixed picture of epidermo-dermal contact dermatitis ensues.†

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*Terra-Cortril®, a product of Pfizer Laboratories, contains terramycin and hydrocortisone; Ilotycin ointment®, a product of Eli Lilly and Company, erythromycin; and Cort-Dome®, a product of Dome Chemicals, Inc., is cream hydrocortisone in an acid ointment base.

†This explanation is simplified, and by no means proven. Several years ago I[16] supported the theory that the protein part of the complete antigen, the so-called carrier or "Schlepper" plays an important part in the process of sensitization and that the chemical nature of the carrier determines the type and phenomenology of the allergy induced. Eisen and his co-workers[17] had suggested that certain

EXPLANATION OF NEGATIVE PATCH TESTS IN THE PRESENCE OF HYPERSENSITIVITY

If only the dermis, the deeper layer of the skin is sensitized, not enough of the allergen may penetrate into the dermis from a patch test to give a positive reaction.* In this case we will encounter a negative patch test in spite of existing contact sensitivity, the latter being demonstrated by positive intradermal tests. One can state definitely that a positive intradermal test proves *dermal* sensitivity; however, the opposite is not correct; a positive patch test does not necessarily mean *epidermal* sensitivity, because if a person has a high degree of dermal sensitivity, then even the small amount of allergen which penetrates into the dermis from a patch test may be sufficient to produce a positive reaction. This apparently is the mechanism of the positive patch test in my cases of neomycin sensitivity. Such an explanation is supported by the clinical appearance of the patch test lesion which consisted of papules and not vesicles, and also by the microscopic examination.

The question arises how neomycin-containing ointments can produce a contact dermatitis when patch tests with the same ointments are negative. It seems plausible to assume that neomycin is more readily absorbed by the diseased skin. This would explain why the neomycin contact dermatitis often appeared only as aggravation of the pre-existing dermatitis. Increased local sensitivity also has to be considered.

CONCLUSIONS AND SUMMARY

1. Neomycin is a very valuable topical antibiotic which can be used with comparative safety, provided one is aware that sensitivity to this drug is not as rare as generally thought.

2. Forty cases of proven sensitivity to topical application of neomycin were observed in private practice during a period of about two years.

3. The clinical manifestation of this sensitivity often appeared only as an aggravation or "irritation" of a pre-existing dermatitis.

4. Intradermal tests with neomycin were uniformly positive, whereas patch tests gave positive reactions in only eleven cases.

*That ease of penetration of the antigen plays a part in eliciting positive patch tests has been shown by Eisen, Orris, and Bellman.[17] The addition of a detergent, such as Tween-80, produced positive reactions with a concentration of the antigen not sufficient to give a reaction in an ordinary solvent.

chemicals can elicit contact dermatitis only if they have the capacity to combine with skin protein; later Eisen and Belman[18] found that simple chemicals apparently vary in their affinity for amino acids, some combining with lysine, others with cysteine. Since then R. L. Mayer[19-21] in a series of fundamental studies, has brought experimental evidence that the type of carrier protein, whether fibrous or globular, largely determines the form of allergy induced.

A more thorough discussion of epidermal and dermal sensitivity will be found in a previous paper[22] dealing with dermal delayed sensitivity to nickel and chromate.

5. Microscopic examinations of both patch and intradermal tests showed that a monocytic infiltrate in the dermis dominated the picture and that the epidermal changes were relatively minor or secondary. This supports the contention that contact dermatitis from neomycin is almost always based on dermal-delayed sensitivity.

ADDENDUM

By the time this article went to press (December, 1957), I had observed well over fifty cases of neomycin contact sensitivity.

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THE TREATMENT OF RAGWEED POLLINOSIS WITH A SINGLE, ANNUAL EMULSIFIED EXTRACT INJECTION. II.

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EFFORTS to shorten the treatment period of pollinosis were first centered upon lessening the number of injections needed to take the patient, usually, to an arbitrarily selected top dose. In 1900, Curtis[1] treated ragweed pollinosis by injection methods and subsequently attempted oral desensitization which he reported as successful. Prausnitz, however, in 1902, gave himself a single injection of pollen extract and suffered a constitutional reaction of which he says, "The results were of extraordinary interest and at the same time, terrifying."

Later, Freeman,[2] based on work initiated with Noon in 1908, suggested fifty-four injections given at intervals of one week to reach a terminal dose of 100,000 Noon units. By 1903,[3] this course of treatment had been modified and, under special circumstances, a "rush" method was used. With the patient hospitalized, increasing concentrations of extract mixed with epinephrine were injected every two hours for five to seven days until a final injection of 80,000 Noon units could be given.

Subsequently the "shock" method was employed.[4] Utilizing the most concentrated extract available, successive doses of 3,500, 7,000, 10,500, 14,000 and so on to 75,000 Noon units were injected every two or three days and finally once weekly with the total number of injections varying from seven to fifteen.

By 1937, the writer had lessened the injections to five in number by assuming an arbitrary first dose based on history and skin tests. He doubled each successive dose administering it with epinephrine. No serious reactions occurred but they were noted more frequently in such patients as compared to those given the traditional type of aqueous injection treatment.

The results were no better and this method was, therefore, reserved for patients who appeared so late in the year that weekly injection treatments could not take them to sufficiently high levels of dosage.

In order to lessen the number and degree of reactions noted following use of aqueous extracts, solutions of pollen have been manipulated in many ways. The literature lists at least twenty-three methods of extracting pollen—either of precipitating and re-dissolving the so-called "active" ingredient or of suspending it in various menstrua in order to slow its absorption.

One such interesting manipulation was reported by Sutton[5] who, in 1923, first used the "repository" type of single injection. He took ground, undried, undefatted pollen placing it in olive oil and reported 80 per cent

of his patients completely relieved and the others moderately improved. He said, "The olive oil delays absorption and the suspension adds the proteins left in the residue of water extracts. Also the slow absorption allows the use of larger doses and decreases the danger of severe reactions." He reported no general reactions in the patients so treated.

On the basis of Sutton's work we used (unpublished data) a dried, defatted pollen extract in buffered saline and emulsified in the ether-soluble pollen oil. Although we did not know the best time to administer the injection or how much pollen extract to use, the results were no better than those achieved with conventional aqueous extracts and the clinical experiment was abandoned, although there were no reactions. Forty of sixty patients wished this type of treatment continued.

In 1947, Loveless, as part of a study concerned with blocking antibody, used a saline extract of dried, defatted ragweed pollen emulsified in corn oil. The dose was determined on the basis of ophthalmic tests. The reaction rate (considering all responses, however mild, as reactions) was estimated at 25 per cent. With the substitution of mineral oil, the number of reactions of all types was lowered to approximately 5 per cent, a level no higher than that seen in her hands with abbreviated aqueous injection techniques employing doses higher than those usually employed in traditional clinical practice.[6] With the use of adequate precautions we[7] found it possible to lower the incidence of reactions to none in thirty-six drug-protected patients with one mild and another second moderate reaction occurring in two unprotected patients. Subsequently, using the same protective techniques in more than 1000 repository injections, only seven allergic reactions were seen as noted as flushing and pruritus in three patients, urticaria and nasal stenosis in three and angioedema and bronchospasm in the seventh. (Data in preparation for publication).

It must be stressed that in the hands of physicians as yet unskilled in the use of the emulsion types of pollen solution mixtures, this method of administration requires the acquisition of new techniques of testing, classifying and treating patients. For the successive ophthalmic tests, the preparation of the patient and the injection of the emulsion in three to five portions, spaced at fifteen-minute intervals, there is needed a minimum of two to four hours with time available beyond these limits (that is, at least two days) for the treatment of possible immediate or delayed constitutional reactions. For the emulsion to be given in a reasonable amount, extracts of the strength of 60,000 Protein Nitrogen Units/ml (preferably 240,000 P.N.U./ml) must be available and free of glycerine if the emulsion is to remain stable. Strict aseptic precautions must be followed with adequate aliquot portions reserved for tests of sterility since the introduction of bacteria into the emulsion leads to abscess formation which may, however, be of the sterile type.

To repeat the essentials of pre-treatment preparation from our first published communication,[7] the patient, after the ophthalmic tests have been completed, is given an antihistaminic agent by mouth and epinephrine (1:1000) 0.15-0.3 ml injected subcutaneously proximal to the site selected for the emulsion injection. Blood pressure and pulse rate determinations are done at intervals of five to ten minutes so that their increase may warn the physician of one type of impending anaphylactic shock, enabling him to take the necessary steps to mitigate it by the use of a tourniquet, epinephrine, again injected proximal to the site of the emulsion depot and either an antihistaminic agent given intravenously or Solu-Cortef® (Upjohn), 50 mg, given intravascularly as well as an adrenergic amine injected subcutaneously into the opposite arm.

For peace of mind it would be well to have available an intermittent positive pressure breathing apparatus with automatic control of respiration and nebulization of epinephrine (1:100) using 60 per cent oxygen and 40 per cent air although we have so far had no need for it.

In clinical practice, the patients are usually given the injection divided into either three, four or five parts in the same injection site and actually through the initial channel made by the hypodermic needle at the time of the first inoculation. Fifteen minutes after the final portion of the injection has been given, Sus-Phrine® (Brewer) is administered by subcutaneous injection in doses of 0.1-0.3 ml into the opposite arm. No delayed allergic reactions have so far been reported, although those patients who reacted while under treatment and who have responded to an antihistaminic agent given at the office, have had recurrences of urticaria for as long as forty-eight hours subsequent to the injection. For physicians who are not properly equipped in office space or who do not possess the suitable apparatus or do not know the technique for handling possible reactions, this type of treatment is not, in its present state, recommended. It is assuredly not for the faint hearted.

As regards patients, it is ideally suited for those in transition from monthly visits to once yearly and for those who present themselves for treatment less than three months before each pollen becomes prevalent and especially in geographical areas in which there are well marked pollen seasons. It is suitable for those whose traveling makes regular visits to the physician impossible. It has so far also been given to those whose distance from a physician's office and whose aversion to auto-inoculation make conventional treatment undesirable. It has been used for the crippled, the incapacitated, the pregnant and for those who by nature are irregular in their attendance; usually those with a high "lapse" rate.

It is planned to publish the results *ad seriatim* for each group of patients. This paper deals with thirty-eight patients treated with material graciously supplied by Dr. Loveless, for the ragweed pollen season of 1957. The successive papers will be concerned with 164 patients treated for tree pollen sensitivity, 380 similarly injected with grass pollen

emulsion and 233 given house dust repository injections. The exact total given ragweed pollen emulsion injections is not as yet available but is approximately 541.

To exclude, in some degree, possible "placebo reactors" no patient who had suffered from typical pollinosis for fewer than three successive seasons preceding the emulsion injection treatment was given consideration, except for one patient seen during the previous ragweed pollen season. Two patients could not remember the exact number of years during which they had responded to ragweed pollen with symptoms, but the duration of their illness was in excess of twenty years. The patients otherwise represent a cross-section of typical specialty allergy practice. Four had been pollen-sensitive for three years and one for four. Thirteen had been ill for six to ten years. Eleven more had presented true pollen symptoms for ten to twenty years and eight for twenty-one to forty-five years.

The total described reaches not thirty-eight but forty because the duration of the two types of pollinosis is reported twice for two patients in whom they were concomitant. One suffered from nasal pollinosis for thirty years and combined nose and lung symptoms for twenty-five years and another obversely with upper respiratory tract symptoms for four years but of lower respiratory tract difficulties and cough and spasm for six. But, in seventeen, nasal symptoms alone were described, and in sixteen, both nasal and pulmonary which in fourteen had on occasions in the past occurred together. In five bronchospasm alone (with minimal nasal symptoms if any) was described as the chief presenting complaint.

The sexes were not equally represented with twenty-four males and fourteen females. The preponderance of male patients is explained by the fact that they, from their point of view, could not or would not take long courses of aqueous injections. We especially favored the selection of adult male patients because, being in the executive group, they could be regarded as more stable and not like female patients, likely to change their social status by marriage or their physiological status by pregnancy or their geographical status as forced by circumstances of their husbands' occupations to leave our area. These male patients represent part of a group to be re-tested annually and if immunity as measured by ophthalmic tests should remain high will then not be treated by injections so that the duration of their immunity as coupled with clinical sensitivity can be observed.

There were five children of whom two were aged ten; one, twelve; and two, fifteen. These were given the emulsion injections because they were difficult to control for weekly aqueous injection treatment. The other patients were representative of all age groups with six less than thirty years of age, fourteen between thirty and forty, and six in the next decade. Two were respectively fifty-one and fifty-four years of age and five between sixty and sixty-five chosen because it was difficult for

them to travel to the physician's office, especially during the winter months.

Ten patients had never had injection treatments, eight had taken injection treatments many years previous to these studies, one twenty-five to thirty years ago. Fifteen had been treated by us. Of these, two had been given only one injection respectively 0.5 and one P.N.U. Eight were "transition patients" who had been given aqueous injection treatments in top doses of 4000-7000 P.N.U. The others had received less than 1000 P.N.U., a relatively low immunizing top dose in our area.

No method for the scientific evaluation of clinical results of the treatment of pollinosis has yet been discovered. As is known from the histories of allergic patients there are natural or spontaneous remissions, in that there are years during which, in the absence of any injection treatments, the patients suffer no symptoms. One wishes that such seasons of freedom could be related to pollen counts (which are less amenable to statistical analysis than clinical symptom evaluations) but unfortunately such periods of remission sometimes coincide with seasons characterized by high pollen counts and exacerbations may also occur during years when "pollen counts" show less pollen to be in the air. Local factors or patient states must, therefore, play some part.

Any form of treatment which depends for its evaluation on patients' descriptions of clinical symptoms must take into consideration "placebo reactors" not only for good but for poor health. Our studies with patients given saline alone would suggest a minimum of 30 per cent. This approximates the results achieved by Loveless with placebo emulsion injections.

A separate group of patients consisting of eighty subjects proved seven to react to saline, one with four successive weekly attacks of asthma. Of this group, twenty-seven patients reported perfect results and the others moderate and good results which they considered as due to the pollen injection treatments. In patients who rebel against injections and are forced to take them, we can predict a 5 per cent failure rate. Some of these resent the injection treatment and go out of their way to prove it inefficacious. Others may resent the treatment but, taking it, report good results so that they can cease treatment with the argument that they would like to see how long the good effects will last.

Within these extremes almost all patients minimize or maximize their responses. A representative patient will report thirty minutes of matutinal symptoms as an excellent result while a second, with a half hour of morning symptoms, complains that the injection treatment had failed to relieve him.

An examination of the literature concerned with treatment of pollinosis as published between 1900 and 1958 shows that all results reported can be grouped within the same limits and are of the same order of magnitude despite the use of more than twenty varieties of extracts, eight types of treatment schedules (including extremely low and extremely high doses) and the use of saline.

These vagaries of response are not applicable to the single injection of pollen emulsion because a number of factors are eliminated. The measurement by ophthalmic techniques of the level of immunity tells the physician where the patient stands as a result of treatment. Placebo reactors can be eliminated. There is no irregularity of attendance. The fact that each patient receives his estimated top dose six to twelve weeks before the pollen season begins makes the measurement of the results less difficult. Financial considerations are at a minimum since patients may report to the office without charge if symptoms require medical treatment.

Objections might be made against the use of the patient as a control for himself. It is true that no two pollen seasons are comparable, but our records show that tallies of prescriptions issued at the patients' requests only vary by a little less than 6 per cent when comparing the "worst" year and the "best." It can be taken for granted that as many will request medication for minimal symptoms as there are those who will ignore symptoms of moderate severity because of a dislike of the idea of taking drugs or of feeling "medicated." It is true that patients forget the misery of yesteryear and exaggerate the improvement of the first year of treatment if only to justify themselves in their own eyes for having decided to take injections. Those who set their hopes high may be somewhat disappointed but generally their reports will be balanced by those who expected little good effect and are pleasantly surprised.

The diminution in the number of patients taking repository injections who request medicine as compared to those on aqueous treatment who have reached approximately the same dose is striking. Of 164 patients given repository injections for tree pollen sensitivity, only two requested medication for relief of symptoms as compared to almost 30 per cent of an approximately equal number taking aqueous injection therapy.

The actual counting of sneezes is of little importance. There is no norm for this natural reaction to irritation of the nares, and non-allergic subjects may vary greatly in why and when they sneeze and how often. And, in addition, allergic patients appear to sneeze non-allergically more often and for less cause than do non-sensitive subjects.

Hours of symptoms are equally difficult to evaluate. A diminution of ten days of usual symptoms to one represents 90 per cent improvement, as does an equal number of days with lessening of symptoms of ten hours to one, and of ten sneezes to one. A patient, in other words, may suffer the same number of days but less each day or fewer days and the same amount of sneezing each day. We are not concerned with the clinical fact that patients sensitive to pollen given pollen extract by injections of any type suffer fewer symptoms than those who are not so treated as we are with how we are to measure the results of treatment for the future as compared to symptoms in the past.

For the present short series it was decided to let the patients speak

for themselves. As far as we know, all but two plan to return to single emulsion injection treatment. One of these may return although the results were poor. The other has been moved to a distant part of the country.

How would a physician interpret these results? I feel that in five patients they were equivocal (Patients: 7, 19, 21, 31, 36) and in five they can be considered poor (Patients: 11, 16, 25, 30, 32). Two patients took prophylactic medicine which although mild makes classification unsatisfactory. But in twenty-eight of thirty-eight the results are as close to complete immunity as present-day standards permit us to determine.

The five patients whose results were equivocal varied in every respect excepting that the dose administered was 5,000 P.N.U. in one and 7,500 P.N.U. for the other four.

We can find no excuse for the poor results such as the giving of the injection up to as late a date as mid-July because some "late patients" did well. Four of these are the least "sensitive" patients and three of the patients received 10,000 P.N.U. Two are sensitive to Alternaria or Hormodendrum or both. Two suffered symptoms while on vacation when they traveled by car and stayed in environments in which dust diminution precautions had not or could not be followed. But the results must be interpreted against the background that one injection only was given in so many patients and on the basis of no previous injection treatment in some and of little or none in others. The "transition" patients could be expected to do well, although in some the dose of aqueous injection extract was small (32, 100, 300, 520, 600 P.N.U.) but treatment had been stopped in almost all patients by June 1 or at the latest, by early July.

Table I summarizes the patient's number in the series, the identifying initials, sex, age and diagnosis as allergic coryza (AC), bronchial asthma (BA) or both. In the list any history of bronchospasm, however slight, classifies the patient as asthmatic, but in the present text, only two are considered presently suffering from asthma since symptoms occurred in the previous year. The duration of symptoms is then given, followed by note of previous treatment, if any; and if none, this is signified by a 0; if any but during previous years and with extract and top dose unknown by the sign + and thirdly, if by us, the top dose in protein nitrogen units.

The results of tests are given in three columns, the first for intracutaneous tests giving the number of protein nitrogen units required for the formation of a wheal, pseudopodia and a flare, and the second, for pressure puncture tests marked +. The results of ophthalmic tests represent the number of units needed to cause caruncular redness checked with the next successive strength placed into the second eye. When the figure 10,240 is followed by a minus sign (—), it is to be taken to signify that

TABLE I. RESUME OF TREATMENT IN THIRTY-EIGHT PATIENTS

No.	Pt.	Sex	Age	DX	Years	Aqueous Injection PNU	Tests—P.N.U./cc			Emulsion Total PNU	Date Given	Patient Comment
							IC	PP	Ophth.			
1	LB	M	35	AC	10	0		+	80	7,500	6/12/57	Some sneezing; no medication
2	AB	F	29	AC	3	0	100		320	7,500	7/ 2/57	Best season ever had.
3	WB	M	14	AC & BA	8	+ 900		+	1280	10,000	6/17/57	Has improved steadily each year.
4	SB	F	42	AC & BA	6	+1000	2000		10240—	10,000	6/17/57	Same perfect results as with conventional treatment.
5	WB	M	38	BA	35	+4000	2000		2560	10,000	6/17/57	A wonderful season.
6	EB	F	60	BA	8	0			10240—	10,000	7/ 9/57	No symptoms.
7	JB	M	42	AC & BA	39	+ 600		+	320	7,500	7/10/57	Some sneezing; no medication.
8	FB	M	42	AC & BA	30	0	100		160	7,500	6/18/57	A perfect season.
9	GB	M	40	AC	16	+ 620	100		320	7,500	7/10/57	Enormous relief compared to previous years.
10	CC	F	31	AC & BA	"years"	0		+	80	7,500	6/11/57	Excellent result.
11	DC	F	37	AC & BA	18	+ 32	2000		10240—	7,500	7/11/57	While on vacation (7/27-8/10) miserable. Well at home until humid spell (Mold Sensitive).
12	EC	M	10	AC & BA	7	+6000	2000		10240	10,000	7/ 2/57	Not one sniffle since repository injection.
13	RC	F	36	AC	28	+4500	1000		1280	10,000	6/17/57	Fine; few morning sniffles relieved by medication; better this year than ever before.
14	BE	F	24	AC & BA	17	+ 40	1000		5120	10,000	6/18/57	A good season.
15	JF	M	12	BA	11	+ 600	2000		10240—	10,000	7/ 3/57	Good for 3/52 then symptoms during rainstorm (Mold Sensitive). Otherwise well.
16	MG	F	37	AC & BA	20	0	2000		10240—	10,000	6/12/57	A little improved; not much nasal difficulty but more asthma; thinks "flu" injection brought on an attack.
17	NG	M	61	AC	6	+ 7	100		160	7,500	7/ 2/57	Very much improved; best season ever had.
18	RJ	M	32	AC	15	+ 400	100		1280	10,000	6/18/57	"Improved over 100%"; eyes clear and sneezes very little.
19	HK	M	15	AC & BA	6	+1000	2000		10240—	7,500	7/11/57	Less cough; no wheezing or hay fever; some sniffles all season.
20	LK	M	25	AC	3	+ 60	100		320	7,500	7/ 9/57	Much better; no medication.
21	AL	F	37	AC	3	+1200	100		160	7,500	7/10/57	Symptoms began 9/2; lasted 3 days; Fine but throat and palate itchy.
22	RL	M	17	BA	10	+4000	1000		10240—	7,500	7/10/57	Excellent health; "didn't even know that the ragweed season was around."
23	HM	M	31	AC & BA	10	+4500	1000		10240—	10,000	7/10/57	"This is the best season I've had in years."
24	JM	F	33	AC	10	+ 520	2000		10240—	10,000	7/ 2/57	"Quite pleased; better than last year."
25	VO	F	47	AC & BA	20	+ 15	2000		10240—	10,000	7/11/57	Hay fever gone; more asthma than usual, requiring more medication which does not last as long for relief.
26	RP	M	41	AC	many	+5000	2000		320	7,500	7/10/57	Good season.
27	CQ	F	61	BA	9	+7000	2000		10240—	10,000	7/10/57	Very well during the season.
28	KR	F	38	AC	20	+ 60	2000		10240—	4,500	7/11/57	Most satisfactory; never had such a wonderful season; most successful.
29	AS	M	63	AC & BA	30	0	1000		40	7,500	7/ 3/57	Symptoms began August; were mild.
30	DS	M	10	AC	6	0		+	40	7,500	7/ 3/57	Worthwhile but not 100% effective; considerably less difficulty this year than last.
31	GS	M	51	AC	3	0		+	20	5,000	7/ 2/57	Hay fever symptoms did not start until Sept. 2; relieved by Diafen.
32	HS	M	28	AC & BA	25	+ 1	2000		2500	10,000	7/12/57	"Filled up" most of the time; wheezing. No night attacks; takes Hyadrine prophylactically.
33	NS	F	25	BA	22	+ 300	100		10240—	10,000	7/ 2/57	"Feel wonderful." Comparatively free of asthma.
34	CT	M	45	AC	10	0		+	160	7,500	6/18/57	Symptoms much the same; not improved much.
35	TT	M	40	AC	20	+ 0.5		+	40	7,500	6/11/57	No symptoms; eyes itched once; no medication.
36	WV	M	54	AC	20	+ 40	1000		40	7,500	6/18/57	Slight sneezing until 8/27; 12-15 sneezes 8/28; one week of symptoms early September.
37	AW	M	62	AC	28	+ 110	2000		160	7,500	7/ 3/57	No symptoms.
38	AW	M	31	BA	1	+ 600	1000		640	7,500	7/10/57	No symptoms whatever; takes Hyadrine prophylactically for asthma.

the ophthalmic test was negative at that level. The total dose given in one site in one injection is then listed with the date given, and then the patients' comments on the results of treatment.

Because of the actual disbelief encountered among physicians, the following statements are made dogmatically and with emphasis for the tenth patient in the list. First, he gave a positive pressure puncture test although he was not tested intracutaneously. He gave a conjunctival response to one drop of an 80 P.N.U./ml solution placed on the lower lid. The actual dose injected at one sitting, in one site, without reaction, was 7,500 P.N.U. Finally, despite the fact that the patient had suffered from allergic coryza and bronchial asthma every year for many years before taking the treatment, he did not experience a single sneeze or wheeze during the ragweed pollen season.

The thirtieth patient, listed similarly, took 7,500 P.N.U. on the basis of a positive pressure puncture test and ophthalmic response to 40 P.N.U. He reported some seasonal symptoms perhaps because the injection was not administered until July the third.

The thirty-first patient with three previous years of seasonal symptoms received 5,000 P.N.U. on the basis of an ophthalmic test at the twenty P.N.U./ml level. His symptoms, usually apparent by mid-August, were delayed until September 2, being severe on that day and so mild thereafter, that for two weeks they could be controlled by a tablet of Diafen® (Schen-Labs) taken as needed. The thirty-fourth patient noted in the table was treated similarly but reported no improvement.

The patients' comments are listed verbatim as given and recorded by a secretary.

In summary, thirty-eight patients suffering from allergic coryza, bronchial asthma or both, due to sensitivity to ragweed pollen were treated with one injection of an emulsion containing ragweed pollen extract. The doses given were 4,500 P.N.U. (one patient), 5,000 P.N.U. (one patient), and otherwise, either 7,500 or 10,000 P.N.U. Ten patients had never before received any injection treatment. The others had been given subcutaneous doses of aqueous extract varying from 0.5 to 7,000 (one patient) P.N.U. In twenty-eight patients, the results were judged to be as near perfect as it is possible to achieve in that the patients did not know that there was a ragweed pollen season. In six, some immunity was perhaps carried over from previous treatment with aqueous extract of which the last injection was given six to twelve weeks before the ragweed pollen season although none had reached the top dose usually needed for good immunity in the New England area although exceptions to this are sometimes seen in that occasional patients do extremely well with minimal doses.

No correlation between clinical sensitivity, ophthalmic responses, skin test reactions, size of dose and immunity could be made.

The next related paper in this series will be concerned with the results recorded in 164 patients treated similarly for sensitivity to tree pollens.

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Grateful acknowledgment must be made of the unstinting efforts of Miss Evangeline Chumacas, Miss Gloria Guarino and Miss Patricia Pepin who enthusiastically and quickly mastered an entirely new pattern of laboratory and treatment techniques, making the changeover to emulsion injection therapy easily possible.

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BASIC BIOLOGICAL RESEARCH

Research not only adds to our knowledge but also supplies an understanding and insight into the interrelationships of knowledge. Science formerly was a means of getting to know the world; now it is enlisted to change the world. It is a dis-service to unify where no unity exists by trying to explain phenomena of different natures on a single basis. Hypothesis must not be confused with proof. Conflicting hypotheses and doctrines stimulate investigation to determine truth. Distraction from the primary purpose or objective of research often causes great inefficiency. The eye must be kept on the target. Even the most precise data are meaningless unless they are directly related to the phenomena under investigation.—Hopps, H. C.: On the philosophy of research. Texas Rep. Biol. & Med., 14:362-371, 1956.

PENICILLIN COMBINED WITH GAMMA GLOBULIN AS A DIAGNOSTIC AGENT IN URTICARIA OF THE SERUM-SICKNESS TYPE DUE TO PENICILLIN

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IN recent years, we have observed an increase in the number of patients developing the characteristic features of urticaria of the serum-sickness type following the administration of bismuth-penicillin-procaine.

In urticaria due to penicillin, the diagnostic skin and passive transfer test reactions to crystalline penicillin are seldom positive, especially in cases of marked sensitivity. In cases of urticaria of the serum-sickness type, a positive diagnostic test reaction is also rarely, if ever, seen.

We have attempted, therefore, to find a more suitable allergen than crystalline penicillin for demonstrating allergy to penicillin. On the basis of analogies with drug allergy, we decided to test combinations of penicillin with proteins (human serum and gamma globulin). Studies with similar combinations have been reported by others,[1,5,6,7,8] although to our knowledge no studies on large groups have been reported.

MATERIALS AND METHODS

1. The reagents used in the investigation and the amounts used for intracutaneous injections were:

(a) *Crystalline penicillin.*—Five hundredths of a milliliter of a solution of 10,000 I.U. of crystalline penicillin in one ml of distilled water (500 U).

(b) *Combined penicillin and human serum.*—Five hundredths of a milliliter of a mixture containing 10,000 I.U. of crystalline penicillin and one ml of human serum. The serum was from subjects who had no history of penicillin allergy and who showed negative intracutaneous test responses to crystalline penicillin and to trichophytin.

(c) *Gamma globulin.*—The gamma globulin was prepared and obtained by courtesy of R. Backhaus; it corresponded to a 10 per cent solution with a degree of purity of 98 per cent. Five hundredths of a milliliter were used.

(d) *Combined penicillin and gamma globulin.*—Five hundredths of a milliliter of a mixture of 10,000 I.U. of penicillin and one ml of gamma globulin. The mixture was kept at 4° C. Although preparations one-day old could be used, the optimal time of use was after seven to ten days. Preparations stored more than three weeks were opalescent and the results with them were unsatisfactory.

(e) *Procaine solution.*—Five hundredths of a milliliter of a one per cent aqueous solution.

2. Experimental tests were made as follows:

(a) Twenty-four patients with urticaria, serum-sickness type, were tested with intracutaneous injections of crystalline penicillin and crystalline penicillin combined with human serum. The results are given in

TABLE I. INTRADERMAL REACTIONS IN GROUP I

Number of Patients	Crystalline Penicillin		Penicillin Combined With Human Serum	
	Immediate	Delayed	Immediate	Delayed
24	1	3	11	5

TABLE II. INTRADERMAL REACTIONS IN GROUP IA

No.	Crystalline Penicillin		Penicillin Combined with Gamma Globulin		No.	Crystalline Penicillin		Penicillin Combined with Gamma Globulin	
	Immediate	Delayed	Immediate	Delayed		Immediate	Delayed	Immediate	Delayed
1	+	0	+	0	21	0	0	0	0
2	+	0	+	0	22	+	0	+	+
3	0	+	0	+	23	+?	0	+?	0
4	0	0	+	+	24	+	0	+	+
5	0	0	+	+	25	0	0	0	0
6	0	0	0	+	26	+	0	+	0
7	0	0	+	+	27	0	0	+	0
8	0	0	+	0	28	0	0	+	+
9	0	0	+	+	29	0	0	+	+
10	0	0	+	+	30	0	0	+	0
11	0	+	0	+	31	0	0	+	0
12	0	0	+	0	32	+	0	+	+
13	0	0	0	0	33	0	+	0	+
14	+	0	+	0	34	0	+	0	+
15	0	+	0	+	35	+	+	+	+
16	0	0	0	0	36	0	+	0	+
17	0	0	0	+?	37	+	0	+	0
18	0	0	+	0	38	+	0	+	+
19	0	0	+	0	39	0	0	+	+
20	0	0	+	0	40	0	+?	0	+

Note: +? means doubtful reaction.

Table I. It is apparent that with the combined reagent a larger number of positive reactions (sixteen) occurred than with the penicillin alone (four).

(b) Three groups of subjects were used in the experiment with combined penicillin and gamma globulin.

Group I consisted of forty-six patients with histories and clinical symptoms of typical urticaria, serum-sickness type, divided into two subgroups: a. Cases 1 to 40 (Table II), and b. Cases K, S, A, B, M, and G (Table IV).

Group II comprised fourteen patients with penicillin allergy of dubious nature or with contact type of penicillin sensitivity, or with histories of manifestations of penicillin sensitivity years ago (Table II).

Group III comprised sixteen subjects with no history of sensitivity to penicillin and negative intracutaneous test responses to crystalline penicillin and to trichophytin, as controls.

TABLE III. INTRADERMAL REACTIONS IN GROUP II

No.	Crystalline Penicillin		Penicillin Combined with Gamma Globulin		Procaine		Remarks:
	Immediate	Delayed	Immediate	Delayed	Immediate	Delayed	
1	0	0	0	0	0	+	Urticaria due to procaine
2	0	0	0	0	0	0	" Gastroenteral complaints
3	0	0	0	0	0	0	" Gastroenteral complaints
4	0	0	0	0	0	0	" Sulfonamide was given too
5	0	0	0	0	0	0	" Sulfonamide was given too
6	0	+?	0	+?	0	0	" Per os penicillin
7	0	0	0	0	0	0	Unilateral edema of eyelids
8	0	0	0	0	0	0	Dermatitis of the face
9	0	+	+	+	0	+	Nurse, dermatitis of the palm
10	0	+	0	+	0	0	" dermatitis
11	0	0	0	0	0	0	" pruritus
12	0	0	0	+	0	0	Eruptions 1 year ago } After
13	+?	+	+?	+?	0	0	Eruption 3 years ago } penicillin
14	0	0	0	0	0	0	Eruption 4 years ago }

All subjects in the three groups were tested by intracutaneous injections of penicillin alone, penicillin combined with gamma globulin, gamma globulin alone, and procaine solution. The results are given in Tables II and III. In addition, some subjects in group Ia and all in group Ib were tested by the Prausnitz-Küstner passive transfer test with crystalline penicillin alone and with penicillin combined with gamma globulin. The results are given in Table IV.

As shown in Table II, of the forty patients in group Ia, penicillin allergy was demonstrated by intracutaneous administration of the crystalline preparation in sixteen patients, and of penicillin combined with gamma globulin in thirty-four, not counting doubtful (+?) reactions. Using penicillin combined with gamma globulin, positive immediate reactions were obtained in thirteen patients, delayed reactions in eight patients, and both immediate and delayed in thirteen patients. Only one patient (Case 29) reacted to procaine. This patient also reacted to penicillin.

As seen in Table III, the reactions to penicillin, respectively to penicillin combined with gamma globulin run, in general, parallel. In Case 12, there was a doubtful delayed reaction and in Case 9, a positive immediate reaction to penicillin combined with gamma globulin. Two of the subjects (Cases 1 and 9) gave a delayed reaction to procaine. None of the subjects in this group nor in group Ia reacted to gamma globulin alone.

The results of the tests with all test substances were negative in the control group (III).

Table IV shows the results of intracutaneous tests made for comparative purpose with penicillin combined with gamma globulin in group Ia and with crystalline penicillin alone in group Ib. In group Ia, four of the twelve patients gave an immediate reaction, four a delayed reaction, three both an immediate and a delayed reaction, and one neither reaction. In group Ib one of the six patients gave an immediate reaction, two a delayed reaction, and three both an immediate and a delayed reaction.

Of the eighteen subjects tested by the Prausnitz-Küstner test (Table IV), nine gave positive reactions and four gave doubtful reactions to penicillin combined with gamma globulin, while only three gave positive reactions, and one, a doubtful reaction to crystalline penicillin alone. All results with gamma globulin alone were negative.

TABLE IV. PASSIVE TRANSFERS

No.	I.C. Reactions Group Ia†		Results of Passive Transfers	
			Using Crystalline Penicillin	Using Penicillin Combined with Gamma Globulin
	Immediate	Delayed		
1	+	0	0	+?
2	+	0	0	0
3	0	+	0	0
8	+	0	0	+?
9	+	+	0	+
21	0	0	+?	+
24	+	+	0	+
27	+	0	0	0
32	+	+	0	+
33	0	+	+	+
34	0	+	0	+?
36	0	+	0	+
	Group Ib*			
K	0	+	0	0
S	0	+	0	0
A	+	+	+	+
B	+	+	0	+?
M	+	+	0	+
G	+	0	+	+
18			3+ and 1+?	9+ and 4+?

Note: Numbers of group Ia refer to patients of Table II.

†Group Ia. I.C. with Penicillin plus Gamma Globulin

*Group Ib. I.C. with Crystalline Penicillin

DISCUSSION

Penicillin combined with gamma globulin enabled us to detect sensitivity to penicillin in many cases that were negative to crystalline penicillin (Table II). In cases of suspected penicillin sensitivity (Table III), penicillin combined with gamma globulin produced no false-positive reactions.

The passive transfer test results with penicillin combined with gamma globulin were positive in all cases that gave positive results with crystalline penicillin. In Case 21, the passive transfer reaction was positive although the intracutaneous test result was negative.

In regard to the intracutaneous test reactions to the penicillin gamma globulin combination, immediate responses were positive in about 75 per cent of the positive cases. When a preparation that had been stored for more than three weeks and had become moderately opalescent was used, an immediate reaction seldom resulted, but delayed positive or doubtful reactions increased. This agrees with previous observations that the purer an allergen protein is, the more likely are the reactions to be of the immediate type. Frequently, both the immediate and the

delayed reactions occurred *in the same person.* We have no explanation for this at present.

Nilzén[4] obtained both immediate and delayed responses to intracutaneous tests in two of ten patients who had urticaria due to penicillin. Mosko et al[3] had previously found no relationship between the two types of reaction in the same patient. Perhaps Mayer's[2] hypothesis concerning chemical substances is applicable. According to this hypothesis, combinations with spherical proteins (albumins, globulins) may lead to immediate reactions and combinations with fibrous proteins (keratins, collagens) to delayed reactions.

Whenever both immediate and delayed intracutaneous reactions were obtained in a patient, the passive-transfer test reaction was also positive. Five patients out of six that gave both immediate and delayed intracutaneous reactions also gave positive passive transfer reactions; the sixth gave a doubtful reaction.

Of the five patients who gave only an immediate intracutaneous reaction, one gave a positive and two a doubtful positive passive transfer reaction. Of the six patients who gave only a delayed intracutaneous reaction, two gave a positive and one a doubtful passive transfer reaction. One patient that gave no intracutaneous reaction gave a positive transfer reaction.† Hence, there was no correlation between the Prausnitz-Küstner reactions and either the immediate or delayed intracutaneous reactions.

SUMMARY

Crystalline penicillin combined with gamma globulin has proved to be more effective than crystalline penicillin alone for diagnosing urticaria of the serum sickness type due to penicillin. In thirty-four of forty cases, positive intracutaneous tests were obtained with the combined testing agent as compared to sixteen with crystalline penicillin alone. In more than three-fourths of the positive cases, an immediate skin response was observed. The combined agent did not produce pseudo-positive reactions in doubtful or negative cases of penicillin allergy and in controls. In nine of eighteen passive transfer tests it yielded a positive reaction, and in four, a doubtful reaction as compared to only two positive reactions and one doubtful reaction obtained with crystalline penicillin alone. Passive transfer tests with the combined agent were successful in all cases in which both the immediate and the delayed intracutaneous reactions were positive.

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We are grateful to Dr. Richard Backhaus (Laboratory of the State Institute of Serum Therapy, Budapest, Hungary) for the supply of gamma globulin.

†The two negative Prausnitz-Küstner reactions in group Ib were obtained with patients that gave a negative immediate reaction and a positive delayed reaction.

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SUBJECTIVE PROBABILITY

"More particularly, our aim in the experimental study of subjective probability and risk-taking is, first, to discover the principles underlying the way we *actually* choose, estimate, predict, judge or take risks and, second, to trace the characteristic changes in these activities during the period of development. We shall see whether judgments based on partial information follow their own psychological rules in more or less consistent fashion and how these rules compare with rules of mathematical probability."—JOHN COHEN and MARK HANSEL: *Risk and Gambling: The Study of Subjective Probability.* Philosophical Library, 1956.

IS SEROUS OTITIS MEDIA DUE TO ALLERGY OR INFECTION?

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BECAUSE of their anatomical continuity, the mucous membranes of the paranasal sinuses, nasopharynx, eustachian tube and middle ear cannot be disassociated. Pathologic processes involving one structure may extend to the other. Thus, it is logical to assume that the lining of the eustachian tube and middle ear reacts much the same way as the lining of the nose and nasopharynx.

ETIOLOGY

Causes of serous otitis media can be allergic or nonallergic.

Allergy may cause fluid to accumulate in the middle ear, a condition which may be seen during the hay fever and rose fever seasons. Foods also can produce a similar reaction. The most common inhalants which cause serous otitis media are house dust, ragweed and timothy. The most common food allergen is milk.

Allergy plus infection can produce the same results. But the infection is superimposed and often masks the underlying allergy. Allergic children are much more prone than nonallergic individuals to respiratory infections of all kinds. Those who have an outpouring of fluid into the middle ear are more apt to have the infection localized in that area. Patients who have their allergies under good control are much less prone to respiratory infections in general and, thus, less likely to experience middle ear involvement. However, patients with high nasal eosinophil smears and mild-to-negative skin test results are difficult to bring under control. As in other types of allergy, the role of bacterial allergy is difficult to evaluate.

Only the allergic causes of serous otitis media will be considered here.

SYMPTOMS

The signs and symptoms of allergic serous otitis media are essentially the same as in cases due to nonallergic factors. The two main symptoms are fluctuating hearing loss and recurrent ear infection. There usually is some evidence of allergic rhinitis. Other evidences of allergy, such as bronchial asthma, atopic eczema or hay fever may be present.

DIAGNOSIS

In our experience, allergic serous otitis media is confined primarily to children. As children grow older, the attacks become less frequent and

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less severe. Serous otitis media often shows marked spontaneous improvement at puberty.

It is often difficult to determine which cases are due to allergy, which to infection and lymphoid hyperplasia, and which to a combination of these factors. The nasal smear is of great value in making this differentiation. In most of our cases which have responded to allergic management, the nasal smears showed over 20 per cent eosinophils.

The presence of other allergies in the individual often is of great help in making the diagnosis. For example, those cases of middle ear involvement which were associated with asthma, eczema or hay fever often responded at the same time as the other allergic conditions. A past history of allergy also is of diagnostic value. Skin tests are of value both in helping to determine whether the physician is dealing with an atopic individual and in tracking down the underlying allergens. As with other allergies, the inhalant tests are most reliable. Frequently, elimination diets are used for detection of food allergens as well as for treatment. Occasionally, circulating eosinophil counts are done to help determine the atopic status. Family history is of help, as is the differential blood smear. Some of our patients were given a trial of antihistamines and experienced temporary improvement in hearing, but audiograms did not show any consistent pattern of diagnostic value.

TREATMENT

In cases associated with clear-cut inhalant sensitivities, hyposensitization injections usually are of value. This is particularly true in patients with high eosinophil responses in the nasal smears and clear-cut skin test reactions. Elimination diets are helpful in the younger individuals, in whom foods may be the main offenders. Our first case, for example, was dramatically cured by the elimination of milk from his diet, and for years afterward we were able to reproduce the hearing loss by feeding milk or milk products.

Many of the allergic cases are associated with infection, so in these both the allergy and the infection must be controlled simultaneously. Thus, adequate doses of antibiotics are used when indicated.

In patients with nasal allergy, the normal adenoid may be considerably enlarged by allergic edema. Swelling of the adenoids from any cause can be easily demonstrated by lateral roentgenograms of the nasopharynx. The administration of an antihistamine may result in immediate temporary improvement. Uncontrolled nasal allergy often results in continued lymphoid hyperplasia and edema, which may be temporarily controlled by irradiation, surgery, or both.

Bacterial vaccines were used in selected cases but the results were difficult to interpret. In some of our cases in which infection was a very stubborn factor, gamma globulin injections were given along with allergic management. The gamma globulin dose was 0.1 cc per pound of body weight, given every four to six weeks. With this combined treatment, we

were able to get some patients under control who seemed to be resistant to all other types of therapy, including surgery and radiation of the nasopharynx. Even in some definitely allergic children, surgical removal of the lymphoid tissue, radiation, or both, were necessary, in addition to allergic management, to bring the patient under control.

ANALYSIS OF CASES

In fifty consecutive cases of serous otitis media which were referred to me as presumably allergic in origin, the average age of onset was four years and the average age at which treatment was started was five years. Of these fifty children, 72 per cent were boys and 28 per cent were girls. This is essentially the ratio which prevails for respiratory allergy in general before puberty.

These fifty cases may be divided into three groups: Group I, which consisted of definitely allergic children; Group II, which showed no definite signs of allergy; and Group III, an in-between group which was almost impossible to classify.

The results of allergic management of Group I were excellent for the most part, only one patient showing a poor result. Sixteen cases, or 32 per cent, fell into Group I. Thirteen of these had marked nasal eosinophilia, ranging from 19 per cent to 76 per cent, with an average of 43 per cent. The other three patients in this group were clear-cut atopic individuals and, I feel sure, will show eosinophils in the nasal smear if taken at the proper time. Two had ragweed hay fever. All of Group I had clear-cut definite skin test results, and all were treated by the usual allergic management method—hyposensitization, food elimination, et cetera. I think that one can almost guarantee a good result on those cases of serous otitis media in which the nasal smear is positive for eosinophils and where the skin tests are definitely positive. The converse is true, also. Fourteen patients, or 28 per cent, had negative nasal smears and negative to very mildly positive skin tests, and all did poorly under allergic management.

I have seen approximately 150 cases since this analysis was made, and I arrived at the same conclusions: serous otitis media accompanied by positive nasal smear plus positive skin tests will respond to allergic treatment.

CONCLUSIONS

1. Allergy is an important etiologic factor in some cases of serous otitis media.
2. The same allergic changes that take place in the nose and paranasal sinuses may occur in the eustachian tube and middle ear.
3. Allergy should always be suspected in chronic middle ear diseases in children until it is ruled out as an etiologic factor.
4. Allergic serous otitis media usually will respond well to allergic management.

Medical Arts Building

HISTAMINE CEPHALALGIA AND ITS RELATION TO MIGRAINE

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HORTON[1] and his associates from the Mayo Clinic in 1939 first described the syndrome now known as Horton's Syndrome, or Histaminic Cephalalgia. Recently, Horton[2] stated that from 1937 to January, 1955, he saw 1,176 patients with this syndrome; 1,023 of these were men and 153 were women. It is, of course, well known that patients are attracted to that clinic from all over the world. Even so, no other investigator has reported more than a very few patients with this condition. Ogden[3] in his recent survey of 4,634 individuals with or without headaches, found Horton's syndrome in only 0.1 per cent (five patients in all). Leider,[6] from the Allergy Clinic of the Walter Reed Hospital, saw seventy-one patients with headaches, of whom fifty-two had migraine and only four had Horton's syndrome.[4]

Hansel,[5] otolaryngologist, finds many cases. It might be stated that the incidence of a headache syndrome varies with the definition laid down by the particular investigator. In his specialty 272 cases of histaminic cephalalgia have been reported out of a total of 701 headache cases, a ratio of about 38 per cent. This is in sharp contrast to only 2.5 per cent (eighteen cases in 710 patients) seen by internists and neuropsychiatrists. Hansel does say that many of his cases are atypical and lack one or more of the usual symptoms or signs.

We ourselves have been searching for cases since Horton's first paper was published. We have been able to collect only three cases in the intervening eighteen years—this small figure represents a very low percentage of the many patients who have reported with migraine or tension headaches or both.

Let us discuss these three cases.

Case 1.—Mr. C. J. M., aged forty, funeral director, was first seen on October 26, 1951. He suffered attacks of pain on the right half of his head, especially the face, with blocking and discharge from the right nostril, and redness, swelling and tearing of the right eye. The symptoms lasted as long as twelve hours, unless relieved by an intravenous injection of dihydroergotamine (DHE 45). Morphine in large doses had been injected, but its effect was not nearly as beneficial as that of the ergot preparation. The symptoms occurred about once a day during periods of attacks. Relief had been obtained after the so-called "histamine desensitizations," and he did well on maintenance doses of histamine until he himself stopped them in March, 1951, seven months before he reported to our office. His last attack began three weeks before we saw him, and with it he had some bilateral difficulty in hearing. Injections of histamine for this recurrence were partially successful.

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This patient also had numerous attacks of so-called sinus trouble, and underwent repeated nasal surgery, including removal of nasal polyps on four occasions.

His pain started close to the right eyeball and spread up to the hairline on the right side and down to the right jaw. He described the pain as throbbing. It was usually followed, in about fifteen minutes, by nausea and vomiting. During an attack, vision in the right eye was poor. The family history revealed no migraine complaints, but listed hay fever and asthma.

The results of a physical examination, including fluoroscopy, showed no abnormality present. The nasal mucosa looked normal during the period between attacks. X-rays of the skull had negative results. The fasting blood sugar was 104 mgs; NPN 42 mg; calcium 11.7 mg. The complete blood counts were within normal limits, with only 1 and 4 per cent eosinophil cells. Findings of two urine examinations were negative. The Kahn test reactions were also negative.

A lengthy series of scratch and intradermal skin tests were done, but the response proved practically negative. There were doubtful reactions with extracts of ragweed and house dust. Reactions to foods, including pork extract, were negative by both techniques, although the patient suspected pork and eggs.

Food elimination and food-feeding trials were carried out at two-week intervals. There were three more attacks while on an egg-free diet. He came to our office without breakfast and was fed two soft-boiled eggs, and an hour later two more eggs. No symptoms resulted.

He was then placed on a milk-free diet, but the attacks continued. When he reported to our office two weeks later no symptoms followed ingestion of large glasses of milk given one hour apart.

On November 28, 1951, he was told to avoid pork and all pork-containing products, including ham, bacon, lard, certain sausages and probably Jello. For the first time, the patient's attacks ceased, and when he reported to our office two weeks later he was symptom free. He was given a pork-feeding test (two cans of pork baby food, one hour apart). About forty-five minutes after the first feeding, a throbbing headache began on his right side, with blocking of his right nostril. There was no eye trouble this time, but nausea followed the pain. About three hours later, the pain was so severe that we injected 1.0 cc dihydroergotamine intravenously. Vomiting and relief followed.

Then the patient related that he had both migraine and histamine cephalalgia. His migraine attacks occurred about every one to three weeks and lasted up to eighteen hours. He took aspirin for this type of headache but no ergotamine.

The patient was instructed, of course, to remain on a pork-free diet, and since then he has been free of migraine and histaminic celphalalgia which were obviously caused by pork. On November 18, 1956 (five years after we first saw him), he reported that he was perfectly well, and his hearing was improved.

Case 2.—Mrs. L. B., aged thirty-four, housewife and furniture saleswoman, was first seen on May 16, 1953. Her history, physical examination, laboratory tests, and skin tests confirmed the diagnosis of histaminic cephalalgia, allergic rhinitis, and migraine, along with fatigue which may or may not have been related to allergy.

The attacks consisted of soreness in the left side of the nose "like pins and needles," sneezing, profuse left-sided watery nasal discharge, plus running, irritation and burning of the left eye, and some itching of the roof of the mouth. There was no severe pain. The spells started suddenly, lasted about thirty minutes, stopped suddenly, and recurred four to five times daily; the rhinorrhea sometimes persisted. (The duration was two years, but the attacks varied from day to day.) Malaise and irritability were present, and symptoms were perennial.

As a child she had one attack of homonymous hemianopsia, causing loss of vision in the left half of the visual field for several hours. In the past nine years, she

had eight or nine attacks which began with similar visual symptoms, with numbness of the mouth, lips, tongue, and occasionally of the extremities, followed by severe, generalized, constant headache and nausea, but no vomiting. During these spells she could not speak as she wanted to, and tried to "beat her head against the wall."

She blamed cigarette smoke, and added that she did not like milk. Her family history revealed relatives with hay fever, asthma, chronic rhinitis and nasal polyps, but none with migraine headache.

The nasal mucosa was moderately pale and boggy. There were no other significant physical findings.

Laboratory data: Urine, blood count, Kahn test, and nasal smear results were negative. Fasting blood sugar was 95, cholesterol 157, NPN 23. The basal metabolic rate was minus 25 per cent.

Skin test results were practically negative, with slight positive reactions to extracts of house dust, cat dander, peas, oat, and cocoa.

The patient was placed on a milk-free diet with immediate relief. Two weeks later a milk-feeding test done in our office reproduced a typical attack: one hour after a pint of milk, the left eye was swollen and tearing, with nasal congestion followed by marked malaise, belching and abdominal cramps. The nose remained blocked and there was nasal discharge for two days; examination showed marked pallor of the nasal mucosa.

This patient did well on a milk-free diet.

Case 3.—Mr. M. S., aged forty-eight, automobile service manager, reported January 11, 1956, with severe histaminic cephalalgia and symptoms suggesting migraine headache. The spells had gradually become worse both in frequency and severity during the last six years. Spectacles were prescribed for eyestrain in 1949, and his attacks ceased for an entire year. The symptoms then returned, however, and on three occasions the glass lenses were changed which gave relief. Six weeks ago the lenses were changed again, but this time the change failed to relieve him and pain became severe.

During the attacks, the pain began in the left nasolabial fold as a burning feeling; then was felt in the left nostril and the left upper teeth. The left eye teared with clear fluid for five to ten minutes after which the eye became inflamed. This was followed by severe pain in the left frontal and left temporal regions radiating to the top of his head, always on the left side. At the onset there is nausea for three to four minutes but no vomiting. The pain in the forehead and temporal regions is excruciating, and despite two Empirin® tablets at each attack, the attacks last thirty to sixty minutes and the pains recur three to four times daily. Between spells he admits feeling well.

He was referred by a competent ophthamologist who reported the results of an eye examination, including visual fields, revealed no abnormalities.

Examination revealed no abnormalities except for a moderate deviation of the nasal septum, and an enlarged prostate.

The urine, electrocardiogram, Kahn test, nasal smear, and blood count findings were normal. The sedimentation rate (Wintrobe), however, increased to 21.5. The cholesterol was 224, glucose 108, and NPN 30.

Skin test reactions were positive for ragweed and shrimp extracts, but we could not correlate these reactions with his symptoms.

He was first given elimination diets, especially with milk, pork, and chocolate, but all these failed. For temporary relief, we were forced to inject ACTH. Later we prescribed prednisone, with excellent results. Meanwhile, because of his high sedimentation rate, we searched for foci of infection, and finally his dentist extracted six diseased teeth. Three weeks after the teeth were removed, the pains disappeared. He has had no recurrence of pain for nine months and is taking no medication.

DISCUSSION

In a recent editorial, Horton[6] stated:

"Histaminic cephalalgia is a distinct clinical entity that usually begins in the later decades of life. It is characterized by a unilateral headache of short duration, generally lasting less than one hour; it commences, and often terminates, suddenly—at its height the pain is associated with watering and congestion of the eye, rhinorrhea or stuffiness of the nostril, sweating, and often visible dilatation of the temporal vessels of the involved side of the head—constant, excruciating, burning and boring pain is an outstanding complaint. It involves the orbital area and the temple, and may extend to the upper jaw, occipital region, neck, and shoulder. Frequent attacks of severe pain may occur twenty times or more a week—the attacks are usually not accompanied by gastrointestinal symptoms or visual disturbances. About 90 per cent of the patients are men over forty years of age. Attacks tend to occur in a series, and remissions and exacerbations occur spontaneously."

Horton adds that, "the subcutaneous injection of 0.35 mg of histamine base often will precipitate an attack identical with the one the patient attempted to describe." This induced attack usually can be aborted promptly by the intravenous administration of 1 cc of dihydroergotamine.

Horton also states, "Histaminic cephalalgia appears to represent a localized anaphylactoid reaction, with both localized and systemic manifestations. During spontaneous and induced attacks, it seems evident that histamine is released from the shocked tissues in the region of the pain and accounts for most local phenomena." For treatment of the spontaneous attacks, he also advises intravenous injections of 1.0 cc dihydroergotamine and notes some relief from inhalations of 100 per cent oxygen.

To prevent attacks he gives what he calls "histamine desensitization," usually by a series of subcutaneous injections of histamine itself. More than 90 per cent of his patients have obtained relief from these injections. Horton himself points out, however, that while the procedure sounds simple it is often fraught with pitfalls. The percentage of success drops sharply with each series of attacks—the injections of histamine are most successful in patients who have not had previous histamine injections.

COMMENT

What does all this mean? Is histaminic cephalalgia a clinical entity? Is it caused by elaboration of histamine at the point of pain? Does the fact that injections of histamine relieve the pain prove that histamine is the cause? Do successful results prove that "histamine desensitization" has occurred?

I wish I could answer all of these questions. I am not sure that histaminic cephalalgia is a clinical entity. In fact, true migraine often has somewhat similar findings (visual prodromata, temporal headache, pain in the eyes, periodicity, complete relief between attacks, etc.). The two disorders can occur simultaneously in the same patients, as in Cases 1 and 2, and nausea occurred in the other patient, even though there was no true migraine.

Horton states that in his syndrome the pains may be in the temple and that there is frequently visible dilatation of the temporal vessels of the involved side. This is exactly what Graham and Wolff[7] demonstrated in patients with migraine, with photographs to show the enlarged temporal arteries; these authors then showed that injections of ergotamine tartrate relieved the pain at the same time that the size of the temporal and occipital arteries diminished. Horton himself states that dihydroergotamine intravenously gives excellent and prompt results in his induced or spontaneous cases of histaminic cephalalgia.

In some respects, Horton's patients do differ from most patients who have typical migraine headaches: (1) most of his patients are men; (2) most of his cases occur after forty; (3) nausea and vomiting are rare; (4) attacks start suddenly and end suddenly.

Is elaboration of histamine the main cause of histaminic cephalalgia? That theory is as vulnerable as the theory that bronchial asthma, hay fever, and other truly allergic diseases are due to elaboration of histamine. The histamine theory has not been proven, despite some strong favorable arguments. The fact that injections of histamine seem to be almost specific likewise does not prove that histamine causes the attacks, nor does success prove desensitization.

Our three cases constitute a strong argument against the histamine theory. In Case 1, pork was found to be the cause, and when the patient did not eat pork, he had no "histaminic cephalalgia" or migraine headache. In Case 2, milk allergy was discovered by avoidance, followed by a trial feeding. Symptoms promptly cleared when the patient followed a strict milk-free diet. The third patient's severe pains were relieved after infected teeth were removed; this patient has been symptom-free for almost a year.

Excellent results were obtained in all three patients. Two of these three were allergic; the third had a focal infection.

Our three cases also elicit comment on the fact that in our experience, Horton's syndrome is uncommon. When it does occur, allergic factors and foci of infection should be considered.

Injections of histamine seem to be successful in almost all of these cases, and these injections should therefore be continued, with the precautions outlined by Horton. In our three patients injections of histamine were not necessary.

SUMMARY

1. Histaminic cephalalgia (Horton's syndrome) is characterized by attacks of excruciating unilateral facial pain, inflammation of the eye and rhinorrhea or blocking of the nose on that side.

2. Three cases are presented, showing relief in one by abstinence from pork, in another by abstinence from milk, and in a third by removal of infected teeth.

3. Migraine headache was also present in two of these three patients.

4. It seems possible and even probable that histaminic cephalalgia and migraine headache are closely related.

5. Although histamine injections usually give good results, this does not prove that elaboration of histamine at the site of pain is the cause of symptoms.

6. The theory that injections of histamine lead to desensitization is likewise not proved.

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UNCERTAINTY

"There is an element of private uncertainty in most of the things we have to decide about in everyday life. In the minor and major situations which we constantly have to face, we have to choose, predict or act on the basis of practical knowledge. A judge and jury weighing the prisoner's innocence or guilt, a scientist assessing his evidence, a politician predicting social trends, and a gambler wondering what stakes to play, all endeavour to draw conclusions out of the uncertainties which they feel about the situation."—JOHN COHEN and MARK HANSEL: *Risk and Gambling: The Study of Subjective Probability.* Philosophical Library, 1956.

ANAPHYLAXIS AND THE NERVOUS SYSTEM. PART III.

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BILATERAL focal lesion of the tuberal region of the hypothalamus protects the guinea pig against anaphylactic shock.[1,2]

We may define our next problem by asking whether it is the first (specific) or the second (nonspecific) phase of the anaphylactic shock that is affected by tuberal lesion. The absence of shock may be caused by inhibition of antibody production, by inhibition of tissue products that cause shock, or by a decreased reactivity of the shock organs in the tuberal-injured animal.

In this paper we report an examination of the production of antibodies and the union of antigen and antibody in the tuberal-injured animal.

I. The Effect of Tuberal Lesion of the Hypothalamus on the Production of Antibodies in Guinea Pigs.

Three methods were used: (1) the Schultz-Dale test; (2) the determination of precipitin levels; and (3) experiments on passive transfer.

*Schultz-Dale experiments:**—In these experiments we used eighty-three guinea pigs weighing 300 to 400 g. We operated upon forty-nine of them using the Horsley-Clarke stereotaxic technique, modified by Szentagotai. The test guinea pigs together with thirty-four control guinea pigs were sensitized subcutaneously on the seventh day after tuberal lesion, with bovine serum globulin containing 33 mg protein/0.5 ml saline. The sensitizations were repeated twice at two-day intervals.

On the seventeenth day after the last sensitization, we bled the animals by cutting the carotids, and carried out Schultz-Dale experiments on the surviving intestines of the animals. Because of the well-known high margin of error of the Schultz-Dale test, we examined several small pieces of intestine and, in addition, checked histamine sensitivity. In every other respect we followed the classic procedure of the Schultz-Dale test.

The results are shown in Table I. The difference in reactivity between the tuberal-injured and the control groups is so large as to be significant without doubt.

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Precipitin Production:—We produced tuberal lesion in twenty guinea pigs, reserving twenty for controls. Seven days after tuberal lesion, we sensitized both groups with 0.3 ml of undiluted horse serum. Fourteen days after sensitization the animals were bled and from the serum thus

TABLE I. SCHULTZ-DALE EXPERIMENTS

Groups	Number of Animals	Schultz-Dale Positive	Schultz-Dale Negative
Tuberal-injured group	49	5	44
Control group	34	26	8

TABLE II. PRECIPITINS IN GUINEA PIGS

Number of Animal	Tuberal-injured Group	Control Group
1	0	800
2	200	800
3	0	1600
4	0	1600
5	0	1600
6	400	3200
7	200	800
8	100	1600
9	0	3200
10	0	1600
11	100	800
12	0	1600
13	400	800
14	0	1600
15	0	3200
16	0	800
17	0	800
18	400	1600
19	100	800
20	0	3200

obtained we determined precipitin by ring test. The results are shown in Table II. To be sure, the ring method of precipitation is not an exact procedure. However, the differences between the tuberal-injured and the control groups shown in Table II can, without doubt, be considered significant.

Experiments with Passive Transfer:—From among forty guinea pigs with an average weight of 300 g to 400 g, twenty were assigned the role of donors and twenty served as recipients. Ten of the donor guinea pigs underwent destruction of the tuberal region. On the seventh day following operation, we sensitized them, together with ten control animals, by subcutaneous injection of 0.3 ml of undiluted horse serum. On the fourteenth day following this injection, we bled both the tuberal-injured and the control donor animals and then intraperitoneally sensitized twenty normal guinea pigs with two to three ml of this serum, depending on the size of the receiving animal. Twenty-four hours after the introduction of antibody we challenged by intravenous injection of 0.5 to 1.0 ml of homologous antigen.

While the transfer experiment with sera derived from injured animals was successful in only two cases, we obtained positive transfer with all sera from the control animals. Thus, in contrast with the control animals, only two tuberal-injured animals disposed of enough circulating antibody to sensitive passively.

All three experiments show that production of antibodies in the tuberal-injured guinea pig is greatly diminished.

II. The Effect of Tuberal Lesion of the Hypothalamus on Antigen-Antibody Union.

On the basis of these results, the antianaphylactic effect of tuberal lesion may seem to be explainable solely by inhibition of antibody production. However, in some of our experiments[2] the tuberal lesion was made on previously sensitized animals (that is, animals provided with antibodies) which also showed lack of anaphylactic reactivity. For this, two alternative explanations are available: (1) the production of antibodies in previously sensitized tuberal-injured animals is inhibited and the antibodies existing prior to turberal lesion had been metabolized; (2) the inhibition of the production of antibodies is not the only way by which tuberal lesion interferes with the anaphylactic mechanism. We proceeded to the examination of this possibility.

An approach seemed to be offered by the technique of the passive anaphylactic shock in tuberal-injured animals. In this case, the inhibition of antibody production does not enter into the experiment.

Homologous passive anaphylaxis.—We divided thirty-nine guinea pigs of an average weight of 300 to 400 g into three groups: (1) thirteen guinea pigs we subcutaneously sensitized with 0.3 ml of undiluted horse serum twice at three-day intervals; (2) we set tuberal lesions in thirteen normal (unprepared) guinea pigs; and (3) thirteen guinea pigs served as controls for Group (2). The thirteen guinea pigs of the first group were bled on the fourteenth day following the second sensitizing injection. By intraperitoneal injection of 3.0 ml we sensitized one guinea pig of Group (2) (tuberal-injured) and one of Group (3) (normal controls) with the serum of each of the donors.

Twenty-four hours after the introduction of the antibody, we challenged by intravenous injection of 1.0 ml of homologous antigen. Out of thirteen tuberal-injured animals, eleven showed no shock, one reacted with mild shock and one with lethal shock. This animal which reacted with lethal shock showed no injury in the hypothalamus on examination of the brain (probably because of some mishap during operation). Of the control animals, ten reacted with lethal shock and three with severe shock.

Heterologous passive anaphylaxis.—We immunized two rabbits as donors by four intravenous injections of 2 to 8 ml of undiluted horse serum in gradually increasing quantities at three-day intervals. Fifteen days

after the last injection, we found the precipitin level of the rabbits to be 1/2560 by ring test. With the antiserum from these animals we passively sensitized eleven tuberal-injured and ten control guinea pigs. The animals operated on were sensitized five days after operation. Each animal received 5 ml of rabbit serum intraperitoneally and was challenged twenty-four hours later with 1.0 ml of antigen given intravenously.

Of the eleven tuberal-injured animals, two reacted with lethal and three with mild shock, while the rest showed no reaction. By contrast, out of ten control animals, nine died in acute shock and only one survived after a fairly severe shock.

It appears that bilateral focal lesion of the tuberal region inhibits not only the active but also the passive anaphylactic shock.

THE EFFECT OF TUBERAL LESION ON THE ANTIBODY LEVEL IN RABBITS AFTER SHOCK

Information was collected on antibody levels after shock in normal and tuberal-injured animals. We chose rabbits rather than guinea pigs for this second series of experiments for the reason that rabbits are good producers of circulating antibody. Moreover, we wished to learn whether the effect of tuberal lesion could be produced in rabbits.

First group:—We injected twenty-one rabbits, male and female, weighing 2.5 to 3 kg, first with 4.0 ml of undiluted horse serum intraperitoneally; two days later, 6.0 ml intravenously; and after three days, 2.0 ml subcutaneously and 3.0 ml by intraperitoneal injection. Eleven of the sensitized animals were tuberally injured on the fifteenth day following the first injection; ten animals were kept as controls. On the fourth day after the tuberal lesion (that is, on the ninteenth day after the first injection) we reinjected intravenously 4.0 ml of homologous antigen into both the animals operated on and the control animals. Immediately before and after the reinjection, we took blood from the tuberal-injured and control rabbits in order to determine precipitin levels.

In Table III we present the reaction after challenge and the precipitin levels before and after reinjection. Eight of the tuberal-injured animals remained without reaction, two reacted with mild and one with lethal shock. As to the control animals, two reacted with lethal shock, five with long-lasting severe shock, two with very mild shock, and one remained without reaction. Both the tuberal-injured animals and the controls had high titers of precipitin before provocation of shock, which declined after the provocation of shock in nine cases to zero, in two cases to half or to a quarter of the original titer.

Second group:—Furthermore, we sensitized ten guinea pigs weighing, on the average, 400 g, by subcutaneous injections of undiluted horse serum. After eighteen days we tuberally injured five of the guinea pigs,

keeping the other five as controls. Both groups were challenged by intravenous injection on the twenty-third day with 1.0 ml of homologous antigen. None of the tuberal-injured animals showed anaphylactic symptoms, while all the control animals died in shock. About an hour after

TABLE III. THE EFFECT OF TUBERAL LESION ON ANTIGEN-ANTIBODY UNION IN RABBITS

Tuberal-injured Animals			
		Precipitin Titers	
Number of Animal	Effect of Reinjection	Before Reinjection	After Reinjection
1	Lethal shock	800	0
2	No reaction	1600	0
3	No reaction	1600	0
4	Mild shock	1600	400
5	No reaction	800	400
6	No reaction	1600	0
7	No reaction	800	0
8	Mild shock	?	0
9	No reaction	?	0
10	No reaction	1600	0
11	No reaction	1600	0

Control Animals			
		Precipitin Titers	
Number of Animal	Effect of Reinjection	Before Reinjection	After Reinjection
1	Severe shock	1600	0
2	Severe shock	1600	200
3	Lethal shock	1600	0
4	Severe shock	3200	0
5	No reaction	1600	400
6	Lethal shock	1600	0
7	Severe shock	800	0
8	Mild shock	800	0
9	Mild shock	1600	0
10	Severe shock	1600	0

challenge we killed the tuberal-injured animals with CO and made Schultz-Dale experiments with small intestinal pieces. From each animal several small intestinal pieces were tested and in each case we also determined sensitivity to histamine. After adding homologous antigen to the bath water of the apparatus, in no case did we observe any contraction of the intestinal preparation.

This experiment was repeated with twenty guinea pigs. Of these, we tuberally injured ten animals; ten served as controls. On the twenty-third day following the sensitization, they were challenged as described in the preceding paragraph. Of the ten tuberal-injured animals, one reacted with severe shock, one with fairly severe shock, two with mild shock and six remained without shock. Nine of the ten control animals died in shock and one recovered after a very severe shock.

As with the first group, Schultz-Dale experiments were carried out. In one out of ten tuberal-injured animals, addition of a homologous antigen to the bath water caused intestinal contractions. Intestinal preparations from ten control animals showed reactivity in two cases.

CONCLUSIONS

The following conclusions can be drawn from an investigation of the mechanism of the antianaphylactic effect of tuberal lesion:

1. Antibody production in tuberal-injured guinea pigs is significantly reduced. This is true both for circulating and tissue-fixed antibodies.

2. In view of the fact that the antianaphylactic effect of tuberal lesion manifests itself in sensitized animals provided with antibody, the inhibition of antibody production cannot be the only effect of tuberal lesion.

3. This conclusion is borne out by our observation that tuberal lesion inhibits not only active but also passive anaphylactic shock in the guinea pig (both with homologous and heterologous antibody).

4. In rabbits, as well as in guinea pigs, anaphylactic reactivity is impaired by tuberal lesion.

5. Anaphylactic challenge produces a marked decrease in circulating, precipitating antibody to a similar degree in rabbits with tuberal lesions and in controls.

6. Sessile antibody is reduced both in nonoperated guinea pigs and those with tuberal lesions to a similar degree. This was shown by testing preparations made from the intestines of challenged animals in the Schultz-Dale apparatus.

7. We conclude from these data that the anti-anaphylactic effect of tuberal lesion is not related to an impairment of the ability of available antibody to react with antigen.

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THE IMPORTANCE OF LABORATORY EVIDENCE

"People are rather unpredictable and don't always die when they are supposed to, and don't always recover when they should. All in all, we must depend heavily on laboratory experimentation for sound and controllable basic principles."—DR. ARTHUR TATUM, Emeritus Professor of Pharmacology, University of Wisconsin.

CLINICAL EVALUATION OF ELIXOPHYLLIN® AND CHOLINE THEOPHYLLINATE IN THE MANAGEMENT OF CHRONIC ASTHMA

Control of the Asthmatic Attack with a Single Oral Dose of Elixophyllin®

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THE XANTHINE derivatives have long been mainstays in the treatment of bronchial asthma. Although the potent bronchodilating property of this group of drugs has been repeatedly demonstrated, both clinically and experimentally, this action is most striking when these agents are given intravenously and intramuscularly. The intravenous administration of aminophylline (theophylline ethylenediamine) in bronchial asthma is often more effective than adrenalin and on occasion has been lifesaving. The oral administration of theophylline and theophylline ethylenediamine, however, is not attended with the same degree of success as the parenteral administration of these drugs in the treatment of bronchial asthma. Absorption from the gastrointestinal tract is poor and large oral doses are not well tolerated.

The introduction of choline theophyllinate offered some advance in oral xanthine therapy. Reports of Gagliani, De Graff, and Kupperman,[1] and Dann, De Graff, Brown, and Kupperman[2] indicate higher blood theophylline levels and better patient tolerance with the use of this salt than with the conventional oral aminophylline tablets. Schluger, Mc Ginn, and Hennessy,[3] however, in a recent report demonstrated that higher blood levels of theophylline were obtained following the oral administration of an alcohol-water solution of theophylline than were obtained with either choline theophyllinate or aminophylline, when the three drugs were given in equivalent dosage. When a dose of 2½ ounces was administered orally (equivalent to 400 mg of theophylline or 500 mg of aminophylline) the blood theophylline levels were higher than those reported by Waxler and Schack[4] after the intravenous administration of 250 mg or the intramuscular administration of 500 mg of aminophylline.

The following clinical investigation was undertaken to determine the therapeutic effectiveness of Elixophyllin,® an alcohol-water solution of theophylline, in the oral treatment of both chronic asthma and acute asthma attacks. In the study of the chronic cases, the results of the long-term administration of the theophylline solution were evaluated on the basis of objective and subjective relief of the signs and symptoms of asthma. In addition, a comparison was made between the results obtained with an equivalent dose of choline theophyllinate, the xanthine compound which in the author's previous experience was most effective in the treatment of chronic asthma.

Elixophyllin®—Sherman Laboratories, Detroit, Michigan.

TABLE I. PATIENT DATA

Severity of Asthma		Age		Sex		Type of Asthma		Duration of Disease	
Mild-moderate	21	12 to 50 yrs.	11	Male	10	Infectious	10	1 to 4 yrs.	10
		50 to 74 yrs.	10	Female	11	Extrinsic	5	5 to 30 yrs.	11
						Mixed	6		
Severe	11	12 to 50 yrs.	5	Male	4	Infectious	5	1 to 4 yrs.	6
		50 to 74 yrs.	6	Female	7	Extrinsic	0	5 to 30 yrs.	5
						Mixed	6		

In the study of the cases of acute asthma, the effectiveness of a single large dose of the alcohol-water solution of theophylline in terminating the paroxysm was evaluated.

SELECTION OF PATIENTS

Chronic Asthma.—(Table I) Thirty-two patients with mild-moderate and severe asthma were selected for this study. They were classified as to the type of asthma, severity, duration, and age and sex. Twenty-one patients had mild-moderate and eleven severe asthma. Of the thirty-two patients, fifteen had infectious, five extrinsic and twelve mixed asthma. The disease had been present in one-half the patients from one to four years, and in the remainder from five to thirty years. There were fourteen males and eighteen females. The ages ranged from twelve to seventy-four years.

Acute Asthma.—This group comprised twenty-four patients, thirteen of whom had infectious asthma, five extrinsic and six mixed asthma. There were eleven males and thirteen females. The ages ranged from fifteen to seventy-four years.

METHOD

The thirty-two patients selected were paired as evenly as possible on the basis of type, severity and duration of asthma, sex and age; and divided into two matched groups of sixteen each. All previous medications were discontinued including adrenal steroids in eight patients. The dosages of the steroids were reduced gradually and the alternate drugs substituted in increasing amounts.

One group received the alcohol-water solution of theophylline, two tablespoonfuls three times daily, and the other group received choline theophyllinate 200 mg four times a day. Both medications were given fifteen minutes before meals. In these dosages, both groups received approximately equivalent amounts of theophylline. The alcohol-water solution of theophylline (Elixophyllin®) contains 80 mg of free theophylline, 3 ml of ethyl alcohol and 12 ml of water per tablespoon. Thus, the total daily dose administered contains 480 mg of theophylline. Each 200 mg tablet of choline theophyllinate (Choledyl®) (64.4 per cent of theophylline) is equivalent to 129 mg of free theophylline. The total daily dosage of theophylline then is equal to 516 mg.

Choledyl©—Nepera Chemical Co., Inc.

Each group was maintained on the original schedule for one month. At the end of this period the medications were interchanged and administration continued for another month. Alternation of medications in the two groups was carried out again for two additional monthly periods. In this manner, both groups received each medication for two separate periods of one month at alternate times.

Acute Asthma.—Twenty-four patients suffering from an acute attack of asthma were treated with a single oral dose of 2½ ounces of the alcohol-water solution of theophylline (400 mg theophylline). Severity of dyspnea, wheezing and cough were estimated prior to treatment. Following administration of the medication patients were re-evaluated every three to five minutes until one-half hour had elapsed. The time of onset of relief of symptoms was noted.

TABLE II. SUMMARY OF RESULTS OF TREATMENT WITH ELIXOPHYLLIN® AND CHOLINE THEOPHYLLINATE IN CHRONIC ASTHMA

Total Patients	Duration of Treatment With Each Drug	Results	
		Elixophyllin®	Choline Theophyllinate
32	2 Months	Excellent 17 Good 7 Equivocal 8	Excellent 4 Good 13 Equivocal 15

RESULTS

Chronic Asthma.—(Table II) Throughout the four-month test period, daily changes in frequency and severity of wheezing and cough were recorded by each patient on specially prepared "score cards." At weekly intervals, the patients were examined and the "score cards" reviewed. Clinical improvement of 75 to 100 per cent was denoted excellent, 50 to 75 per cent good, and less than 50 per cent as equivocal results.

With the use of the alcohol-water solution of theophylline during the two separate one month periods, seventeen of the thirty-two patients had excellent results. Of the remainder, seven patients had good results while in eight patients the results were equivocal.

It is interesting to note that of the eight patients in this group who were previously refactory to all therapy save adrenal steroids, two patients could be maintained satisfactorily on the alcohol-water solution of theophylline alone and in another patient the dosage of the steroid could be reduced. In the remaining five patients, Elixophyllin® proved ineffective and steroid therapy had to be reinstituted. These are included in the group which had equivocal results.

When the same thirty-two patients were treated with choline theophyllinate, four had excellent improvement, thirteen good and fifteen equivocal results. None of the eight patients previously treated with adrenal steroids responded significantly to treatment with choline theophyllinate.

TABLE III. RESULTS OF A SINGLE ORAL DOSE OF FIVE TBSPS. OF ELIXOPHYLLIN® IN ACUTE ASTHMA

Patient No.	Sex	Age in Years	Type of Asthma	Response	Time of Onset of Relief After Medication in Minutes
1	M	40	Infectious	Equivocal	—
2	F	58	Infectious	Good	15
3	M	31	Infectious	Good	10
4	M	72	Mixed	Complete	15
5	F	58	Extrinsic	Complete	10
6	M	64	Infectious	Complete	3
7	M	65	Infectious	Complete	12
8	M	59	Extrinsic	Complete	8
9	M	55	Infectious	Good	15
10	F	29	Extrinsic	Good	10
11	M	37	Mixed	Complete	10
12	F	50	Infectious	Good	15
13	F	53	Infectious	Complete	5
14	F	54	Infectious	Complete	25
15	F	60	Mixed	Complete	20
16	F	15	Extrinsic	Complete	10
17	M	60	Infectious	Complete	15
18	F	37	Mixed	Complete	7
19	F	29	Extrinsic	Complete	10
20	F	37	Infectious	Complete	5
21	M	45	Infectious	Complete	10
22	F	41	Mixed	Complete	10
23	F	36	Mixed	Complete	10
24	M	74	Infectious	Complete	6

Acute Asthma.—(Table III) Of the twenty-four patients suffering acute asthmatic attacks who were given a single, large dose (2½ ounces) of the alcohol-water solution of theophylline, eighteen had an excellent result and five experienced good relief. One patient failed to respond. The average time of onset of relief in the patients who responded was eleven minutes.

Side Effects.—There were few gastrointestinal side effects noted following the use of either medication.

DISCUSSION

The advantages of a theophylline preparation that may be given orally and yet produce therapeutic blood theophylline levels as promptly and efficiently as aminophylline administered intravenously[3,4] are many, both to physician and patient. An excellent example of this is the successful termination of the asthmatic attack occurring within thirty minutes which was observed in twenty-three of twenty-four patients. These results are in essential agreement with the results reported by Spielman,[5] Schluger, McGinn and Burbank,[6] and Kessler.[7] The reasons for the rapid absorption of the theophylline in the alcohol-water solution is probably the larger absorptive area available to the medication in a liquid phase plus the enhanced absorption secondary to the alcohol-induced hyperemia in the gastrointestinal mucosa.

That Elixophyllin® proved more effective than choline theophyllinate in the management of chronic asthma may be attributed to the production and maintenance of higher blood theophylline levels. According to Schluger, Mc Ginn and Hennessy,[3] mean theophylline levels at fifteen minutes,

thirty minutes, one hour, two hours, and four hours, respectively, after the oral administration of 5 tablespoonfuls Elixophyllin were 8.0, 10.3, 11.1, 9.9, and 7.1 micrograms of theophylline per ml of whole blood. Following three 200 mg tablets of choline theophyllinate, the mean values obtained at the same times were 0, 0.2, 2.2., 5.5 and 6.6 micrograms of theophylline per ml of whole blood. In the dosages administered each preparation was approximately equivalent to 400 milligrams of theophylline.

SUMMARY

1. The repeated oral use of the alcohol-water solution of theophylline in thirty-two patients with chronic asthma elicited excellent response in seventeen, good response in seven and equivocal response in eight. Of the eight patients who had equivocal results, five had responded previously to none of the medication administered except steroids.

2. The oral administration of equivalent doses of theophylline in the form of choline theophyllinate to patients with chronic asthma produced four excellent results, thirteen good and fifteen equivocal results. All eight patients who had been previously taking steroids obtained no significant response with choline theophyllinate.

3. A single oral dose of five tablespoonfuls (2½ ounces) of Elixophyllin® successfully terminated the attacks in twenty-three of twenty-four patients with acute asthma. Within thirty minutes dyspnea was controlled, wheezing markedly cleared and prolonged respiration significantly lessened.

4. Gastrointestinal side effects were few following the use of either medication.

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AVENUES OF RESEARCH IN ALLERGY

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FUNDAMENTAL research in allergy may have been hampered in the past by lack of central agencies for financial support of such research and the training of allergists. In 1953, the American Foundation for Allergic Diseases was founded, after several years of spade work, by the joint effort of the American Academy of Allergy and The American College of Allergists. The purposes of the Foundation are to encourage research in allergy, training of allergists and education of the public concerning allergic diseases.

In 1956, the National Institute of Allergy and Infectious Diseases was established within the framework of the National Institutes of Health. This new institute, replacing the former National Microbiological Institute, will sponsor well planned basic research in allergy, at both the clinical and laboratory levels.

It is to be hoped that the Foundation and the Institute will complement each other in various phases of the endeavor to increase and improve research and education in allergy, an effort which should lead ultimately to better fundamental understanding of allergic disease and thus to more accurate diagnosis and more effective treatment of patients.

On December 1, 1955, the Foundation announced its three-point national program of (1) fundamental research, (2) medical education and training and (3) public education. Six areas of research were established as most worthy of further investigation. These are (1) ways in which cells of the body are affected by antigen antibody reactions, (2) ways in preventing antibody formation, (3) histamine metabolism, (4) enzymes, (5) autosensitization and (6) collagen diseases.

A review of the investigations previously reported by others is indicated before research is inaugurated. Such review is the *avenue* to any area of research. Keeping abreast of the medical literature is difficult and time-consuming, particularly for the part-time investigator-practitioner, but is basic for good research. Herein is presented a review of selected pertinent literature of 1955 and the first quarter of 1956 pertaining to each area listed by the American Foundation for Allergic Diseases.

WAYS IN WHICH CELLS OF THE BODY ARE AFFECTED BY ANTIGEN ANTIBODY REACTIONS

The avenue of this area has been traveled more than any of the other five and rightfully so, since it became apparent about fifty years ago that

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Dr. Hampton was President, 1955, The American Academy of Allergy.

Presented, in part, at the 12th Annual Congress of The American College of Allergists, April 18-20, 1956. New York.

animals may respond with an altered reaction upon reinjection with a substance ordinarily harmless upon the first injection. Throughout the past fifty years, this avenue has been divided into two roads, one concerning the cellular-histamine theory, originally introduced by Friedberger[61] and studied extensively by Dale[41] and his various co-workers; and the other concerning the humoral-anaphylatoxin theory, proposed by Vaughan and Wheeler[194] and by Biedl and Kraus,[15] who first demonstrated peptone shock in dogs and guinea pigs.

During the past year, numerous reports have appeared in the literature on this subject. Coons,[37] continuing his work with fluorescein-labeled antibodies, reaffirmed that such techniques can specifically localize antigenic material in tissue cells. When sections of lymphoid tissue from immune animals were exposed to a dilute solution of specific antigen, antigen was bound by the antibody in the tissue cells. When excess antigen was washed away, the deposited antigen was then detected by specific labeled antiserum and the antibody in the tissue cells visualized.

Freund[59] with various co-workers, continuing his work with adjuvants, found that when an injection site in the guinea pig's skin was excised one hour after the injection of an emulsion of rabbit spinal cord and adjuvant, the animals developed allergic encephalomyelitis and tuberculin sensitivity. He concluded, therefore, that when antigen combined with "complete" adjuvant is injected, antigenic stimuli may arise, not only at the site of the injection but also in other foci.

Rice[149] supported the use of adjuvants when she reported that guinea pigs sensitized by antigen and adjuvants developed more acute shock and showed a more pronounced and rapid fall in complement titer, when challenged, than those sensitized by antigen without adjuvant incorporation.

Dixon and his associates[46] continued their studies using S^{-35} labeled amino acids with radioactive isotopes as antigen labeling agents, and found that the rate of antibody synthesis increased while antigen was circulating, and declined rapidly after elimination of detectable circulating antigen, in all three stages of responses in the rabbit to bovine gamma globulin. They also observed a relative persistent source of antibody production which appeared after repeated stimulation and increased in proportion to the number of repeated stimuli. In another report,[45] they found that previous immunization with one antigen would accelerate and magnify the immune response to the first injection of another antigen if the two antigens were related, such as human serum albuminin and bovine serum albumin or bovine globulin and canine globulin, but not if the two antigens were unrelated, e.g., crystalline egg albumin and diphtheria toxoid. Also working with I^{-131} and S^{-35}, Francis and his co-workers[57,58] studied the reaction between a sulphone-ovalbumin antigen and antibodies to iodinated-sulphone-globulins and between the resulting precipitate and an iodinated protein antigen.

Campbell and Garvey,[28] using S^{-35} labeled sulfanilic-azo-hemocyanin

antigen, detectable in the liver of animals for at least four months after a single intravenous injection, found that less antigen persisted in the livers of animals receiving multiple injections. Furthermore, an initial injection of labeled antigen followed by several injections of unlabeled antigens resulted in rapid loss of labeled antigen when the concentration of circulating antibody reached 100 μg per ml of serum. The retained antigen rapidly lost its ability to form insoluble complexes with precipitating antibody, but retained its ability to combine with antibody to form soluble complexes. It was suggested that these retained antigen fragments, having physical properties different from those of the injected material, are the actual templates involved in antibody formation.

Johnson and his associates,[97] using massive antigen (bovine albumin) dosage and quantitative antibody nitrogen technique, studied antigen elimination and antibody production and suggested that the breakdown and removal of an antigen from an antibody forming site may be a necessary prerequisite to antibody formation.

Sehon and his co-workers,[163] by starch electrophoretic separations, found the skin-sensitizing antibody to reside in the beta and gamma globulins of serum, the albumin and alpha globulins containing none.

Cooke and his associates,[35] using electrophoretic and chemical studies, found the blocking antibody in human sera resulting from hyposensitization treatment with ragweed pollen extracts, not to be contained in albumin or alpha-1 globulin, but chiefly, in gamma globulin, although their studies could not rule out that some portion of the blocking antibody might reside in alpha-2 or beta globulins. Their findings, however, indicate that blocking and sensitizing antibodies are chemically different entities.

The findings of Loveless and Cann[119] agreed with those of Cooke et al, and pointed out that the blocking antibody has a much lesser mobility than the faster moving skin sensitizing antibody.

Kuhns[111] described a technique for measuring skin-sensitizing diphtheria human antitoxin, produced by injections of diphtheria toxoid, the specificity of which is based upon the ability of the antitoxin to remain at skin sites and later neutralize the delayed specific toxic effects of intradermal Schick test reagent.

Cole and Favour[32] demonstrated that antibody to tuberculoprotein and to tuberculopolysaccharide reside in different fractions of serum. The former passively transferred to guinea pig skins a delayed type of skin sensitivity to tuberculin PPD while the latter transferred systemic anaphylaxis and an urticarial type of skin reactivity and was shown to contain Middlebrook-Dubos antibody. The presence of the tuberculopolysaccharide inhibits passive transfer of the delayed type sensitivity by the tuberculoprotein.

Epstein and his associates[50] using serum of patients with rheumatoid

arthritis and Cohn Fraction II of human gamma globulin, were able to obtain positive direct precipitin tests.

Herberts[84] reported that anaphylactic shock in guinea pigs to egg albumin resulted in hemoconcentration with a 25 per cent fall in plasma proteins, indicating an increase in protein content of extracellular fluids. There was a 40 per cent increase in the protein concentration of the lung with increase in lung weight. The fibrinogen concentration of the blood remained constant in relation to plasma protein levels.

Lawrence[113] in 1950 first transferred tuberculin sensitivity to human skin by using blood leukocytes. During the past year, contributions have been made on this subject.

Cummings and his associates[40] were able to transfer tuberculin sensitivity to normal guinea pigs with an extract prepared from cells of peritoneal exudates and spleen disrupted by sonic vibration. They pointed out that freezing and thawing of human leukocytes yields an active principle, whereas similar treatment of animal leukocytes abolishes their capacity passively to transfer tuberculin sensitivity.

Tremain and Jeter[190] reported passive cellular transfer of hypersensitivity to serum antigens from donors sensitized to the point of typical Arthus reactions, by intravenous, intraperitoneal, subcutaneous, and intracutaneous routes of administration. The sensitivity was demonstrable by cutaneous reactivity, but not by circulating antibody (precipitin tests) or anaphylaxis in the guinea pigs.

Stoner and Hale[179] transplanted thymus and Peyer's patch tissue from tetanus immunized mice into the anterior chambers of eyes of mice. The intraocular transplants exhibited a recall antibody response when the recipient mice were given intravenous injections of the specific antigens.

Rosenthal and co-workers[155] were unable to induce eczematous hypersensitivity in the skin of guinea pigs with leukocytes from the blood of patients clinically sensitive with positive patch tests to resorcin, paraphenylenediamine and nickel sulfate.

Askonas and Humphrey[7] reported that granuloma tissue from rabbits, immunized with ovalbumin was found to incorporate ^{14}C-glycine into the anti-ovalbumin during incubation *in vitro*, but not into rabbit pneumococcal antibody added at the start of incubation, and concluded that incorporation of ^{14}C-aminoacids into the soluble antibody and gamma globulin fractions occurs only when the incubated tissues produces these proteins.

Askonas and White,[8] taking advantage of the property of various tissues, from guinea pigs, immunized with ovalbumin, to incorporate ^{14}C-glycine into the anti-ovalbumin, found that the lymph nodes remote from the site of injection of the antigen to have the highest activity. Lymph nodes, spleen and bone marrow possessed more activity than other tissues, including liver and lungs, and there was a good correlation (except for bone marrow) between the number of antibody-containing plasma cells

seen in tissue sections and the ability of unit weight of the different tissues to form anti-ovalbumin *in vitro*. More plasma cells were noted in remote lymph nodes than in those immediately draining the antigen injection site.

Germuth and his co-workers[66] continued comparative histologic and immunologic studies in rabbits of induced hypersensitivity of the serum sickness type. When animals sensitized with bovine albumin and egg albumin were injected intravenously, bovine albumin was eliminated more rapidly than in unsensitized animals. Qualitative and quantitative differences between the histologic responses of the sensitized and unsensitized animals were observed, adding further support to the hypothesis that the lesions occurring after injection of foreign protein are the result of antigen and antibody combination.

Interest in the role of the eosinophil in anaphylaxis and allergy has continued since Vallery-Radot and his associates[193] published a full report on eosinophilia in anaphylaxis in 1926.

Recently, Herberts[83] injected a specific antigen in a gum mixture intraperitoneally into sensitized guinea pigs and instead of an anaphylactic reaction, a local reaction ensued, consisting of the production of an exudate in which eosinophils predominated. The eosinophils thus obtained showed no proteolytic activity in the presence of the specific antigen. He concluded that eosinophils play a secondary part in anaphylactic shock, acting as agents for the disposal of waste products of proteolysis in the shock organ.

Spiers and Dreisbach,[172] studying cellular response of peritoneal fluid of sensitized mice to specific antigens, found a significant increase in mononuclear cells and a marked increase in eosinophils during the first ten days as well as a slight increase in blood lymphocytes and monocytes and a more significant increase in blood eosinophils. The number and proportion of eosinophils were found to be consistently higher in adrenalectomized animals.[173] They concluded that the eosinophil must be considered along with the plasma cell, lymphocyte and reticuloendothelial cell as a possible source of antibodies. Spiers[171] has reviewed recently the subject of the function of eosinophils and basophils with 245 references.

Swineford et al[181] was able to maintain Arthus desensitization for ten to fifteen days in rabbits with daily injections of specific antigens. Such has not been reported previously. Britton and Coombs[22] using a "coated tanned red cell" and a "red cell linked antigen" technique, were able to demonstrate, serologically, in the sera of grass extract-treated patients a heat-stable antibody that the authors presumed to correspond to the blocking antibody first described by Cooke and his co-workers.[34]

Aladjem and his associates,[2] by chemical means were able to precipitate the active skin-sensitizing antibody factor from human serum with seventy per cent saturated ammonium sulfate, whereas the skin sensitiz-

ing factor of lower animal serum was precipitated between 33 and 35 per cent. They were able to sensitize normal human skin with the precipitates of sera from patients with clinical sensitivities but whose whole serum failed to show skin sensitizing antibodies. Beiser, Dworetsky, Smart and Baldwin,[11] using the agar precipitin technique, were able to show antibodies in human serum to materials derived from *Staphylococcus aureus* but not *S. albus.*

McMaster and his associates,[126] continuing their studies on the persistence of antigenic material injected into animals, reported that, following single intravenous injections of a foreign protein antigen, bovine gamma globulin, into mice and rabbits, antigenic material, persisting in the liver, could be detected for several weeks. Ground liver tissue, taken from the mice and rabbits, either four or six weeks after injecting the antigen, when transferred repeatedly at two or three day intervals to the peritoneal cavities of normal, unilaterally adrenalectomized, recipient mice, rendered the recipients sensitive to active anaphylaxis when they were challenged after a suitable interval by intravenous injections of the original antigen. The authors conclude that their findings throw some light on the state of the antigenic material that persists for four to six weeks in the liver of donor animals, which apparently remained sufficiently unchanged to engender in the recipient mice antibodies capable of reacting with the original antigen. Benacerraf and his associates[12] found the latent period of sensitization of passive cutaneous anaphylaxis of the guinea pig to be inversely proportional to the amount of antibody injected intravenously to sensitize the animal. The injection of very small doses of histamine intradermally, or the local treatment with mild irritants, brought about, preferentially, the appearance of the reaction of passive cutaneous anaphylaxis at the treated site. They concluded that small doses of histamine or other mild inflammatory agents are able therefore to bring about the local fixation of circulating antibody.

Chase, Dameshek, Haberman, Samter and Squier,[30] in a panel discussion, presented pros and cons of the role of the lymphocytes, red blood cells, neutrophils, eosinophils and platelets in allergy and hypersensitivity.

Eisen and his associates,[48] continuing their studies on hypersensitivity to low molecular weight substances, found that the 2, 4-dinitrophenyl group, combined with proteins through azo linkage or by substitution in free amino groups, revealed precipitin curves resembling those of high molecular weight antigens. They reported that, whereas dinitrophenyl-azo-albumin was a less effective precipitant than the conjugated ovalbumin in which dinitrophenyl groups were substituted in free amino acids groups, the former was relatively more effective in precipitating antibody from antisera to dinitrophenyl-azo-proteins than from antisera prepared against amino-substituted dinitrophenyl-proteins. Taliaferro and Talmage,[185] using amino acids labeled with S^{35}, given to donor rabbits during the three-day incubation period following a second injection of bovine albumin antigen,

found that the serum of the recipient rabbits, receiving splenic cells from the donor rabbits, showed no appreciable radioactivity in the precipitin formed by the specific antigen. They concluded that almost all of the sulfur-containing amino acids present in the precipitating antibody were drawn from the amino acid pool during the rise of the antibody and not during the first three days after antigen injection.

Burdon[24] has reviewed quite recently the present status of the cellular and humoral theories of anaphylaxis, and pointed out that both humoral and cellular factors contribute significantly to the chain of events following antigen-antibody union, but stated that neither theory offers a fully satisfactory explanation for the intimate mechanism of the primary injury or for the basic conditions which determine the existence of a hypersensitive state as contrasted with a desensitized state.

Kahn[102] presented a comprehensive discussion of tissue responses in immunity, in which he states that it is difficult to interpret tissue responses in infection and immunity on the basis of tissue hypersensitivity. Gabrieli[62] reviewed the reticuloendothelial activity during antibody response.

In a consecutive series of four recent articles in *The American Journal of Medicine,* reviews on this general subject have appeared on the genesis of antibodies by Harris and Harris,[79] types and distribution of antibodies by Kuhns,[112] the delayed type of allergic inflammatory response by Lawrence,[114] and diagnostic methods for allergic diseases by Sherman.[165]

It is obvious that great strides have been made in this area of ways in which cells of the body are affected by antigen-antibody reactions, and yet we do not have the final answers. As stated by the American Foundation for Allergic Diseases, "Treatment which will ultimately curb, halt or prevent allergic reactions will depend upon a thorough knowledge of the affected cells."

WAYS OF PREVENTING ANTIBODY FORMATION

The prevention of antibody formation has been attempted by various means, the majority of studies having been made in the experimental animal. As early as 1915, Hektoen[81] demonstrated that total body exposure to ionizing radiation suppressed the usual antibody response in experimental animals to antigens injected just prior to or shortly after irradiation. Hektoen and Corper,[82] in 1921, showed that nitrogen mustards inhibited antibody formation. Swift,[180] in 1922, and his associates,[44] in 1928, reported that salicylates suppress antibody formation in rabbits and in human subjects.

When the antihistaminic drugs appeared, reports in the literature of 1946 through 1949, including those of Arbesman and his associates,[3] Leya,[116] Meier and Bucher,[128] Scherer, W. F.,[161] and Dammin and associates,[42] indicated that the formation of antibodies was not affected by these drugs.

Dicumarol and heparin were tested for their inhibitory effect by Forman and her co-workers[56] and Dammin and associates,[57] respectively. Such anticoagulants depressed antibody formation only slightly, but did tend to inhibit *in vitro* antigen-antibody combination.

With the advent of purified steroid compounds many studies have been undertaken to relate their effect to antibody responses. The initial observations resulted[31,47,200] in the conclusions that ACTH or cortisone increased antibody production. Kass and Finland,[106] in 1953, reported that adrenal steroids were very effective in suppressing antibody formation. It is recalled that the dosage and method of administration of the steroids, the type of antigen antibody reaction evaluated, the degree of sensitivity, and the means of measuring differences of antibody, all seem to contribute to variation of the reported results, to be discussed below.

In reviewing the literature of 1955 and 1956, much has been found to supplement the original studies just cited. The unexpected findings of Graham and his associates[70,71] were that focal irradiation of the site previously injected with antigen, in rabbits, enhances antibody responses and maintains the titers longer.

Jaroslaw and Taliaferro[95] reported that HeLa cell mince or extract and yeast autolysate, when injected with sheep red cell antigen in rabbits one day after total body irradiation could restore antibody-forming capacity. Normal rabbit kidney mince or extract, and normal rabbit muscle mince or extract were ineffective. Normal rabbit spleen preparations were ineffective when injected into irradiated rabbits twenty-four or forty-eight hours prior to injection of antigen.

Recently Fitch and associates[55] found that total body irradiation of rats within four days after intravenous injection of antigen caused a depression of the peak of antibody. This depression became more marked as the interval between irradiation and antigen injection was shortened. Irradiation one and six days before antigen injection completely abolished antibody formation.

Roberts and Dixon[151] were able to demonstrate that when lymph node cells from immunized rabbits were transferred to irradiated recipient rabbits, a secondary immune response could be elicited when the recipients were challenged with antigen. When cells from nonimmunized donors were transferred to x-radiated recipients, no immune response was obtained upon antigenic stimulation. Furthermore, when cells from normal or immunized donors were incubated with antigen, then washed and injected into recipients, there was no detectable antibody production.

Colchicine had been reported previously to have an inhibitory effect on antibody formation.[51,56] Tanaka and Coons[186] reported that when full doses of colchicine were administered at the same time as the second injection of antigen into rabbits, there was a pronounced increase in the amount of antibody on the eighth day thereafter. They also found that cholchicine did not produce this effect when injected two

days before or after injection of antigens. These authors postulate that colchicine stimulates the division of the primitive cells from which the antibody sensitizing cells spring.

Delaunay and de Roquefeuil[43] reported that the sensitizing power of horse serum in guinea pigs could be modified by the chemical treatment such as with sodium salicylate, salicylic derivatives, guanidine, and urea.

Stern and his associates[177] found that polyvinyl pyrrolidone was capable of depressing immune hemolysin levels in mice. This effect varied with the strain of mice, timing of the injection, type of antigenic stimulation and the molecular size of the compound.

Using tissue culture techniques, Mountain[136] studied the antibody production by rabbit splenic tissue and the effect of certain chemicals and drugs. She found that antibody production *in vitro* required oxygen, was suppressed by certain concentrations of sodium cyanide, manganous sulfate, ferric chloride, cupric sulfate, sucrose, selected essential amino acids, and cortisone. Experiments demonstrated that the various agents acted by inhibition of some phase of antibody formation by the surviving cells in culture rather than by destruction of antibody once formed.

Recent studies by Newsom and Darrack[138] compared the effects of certain corticosteroids and related compounds on the production of circulating hemolytic antibodies in the mouse. Of six C_{21} steroids tested under the experimental conditions used, they found that the ability to exert a hemolytic antibody suppressing effect depended upon the structure of C_{11}. Variations at the C_{17} position had little effect.

Kass, Kendrich and Finland,[107] measuring antibody nitrogen quantitatively, found that hydrocortisone markedly depressed antibody formation, whereas corticosterone in doses four times as large exerted no significant effect. Corticotropin behaved similarly to corticosterone in a certain dosage but, when greatly increased, had an effect similar to hydrocortisone. Corticosterone did not antagonize the effect of hydrocortisone on antibody production but seemed to act additively to it.

Berglund,[13,14] studying the effect of cortisone on the production of hemolysin in rats given a single intraperitoneal injection of sheep erythrocytes, reported inhibition of antibody formation when the cortisone was given on or before the injection of the antigen. He also found that the antibody response after a large antigen dose was less affected by cortisone than that after a small one. He noted a striking temporal similarity between the effects of cortisone and x-ray on antibody production.

Stern and Davidsohn[176] found that while estrogen was found to enhance the production of immune hemolysin for sheep cells in a certain strain of mice, a moderate inhibition occurred in a strain with high mammary tumors and low antibody. However, cortisone depressed antibody titers in the tumor mice more effectively than in the nontumor, high-titered mice.

Kaliss, Hoecker and Bryant,[103] also working with tumor-bearing mice, but using three different tumor extracts as antigens, found that cortisone inhibits antibody production when injected simultaneously with any of the three tumor extracts during primary immunization. Cortisone had no effect on the secondary response when it was administered during re-immunization to sensitized mice.

Havens and his associates[80] found that antibody formation was augmented by removal of a large portion of the liver.

Hanan and Germuth[77] found that rabbits previously exposed to bovine serum albumin at an early age are rendered incapable of producing antibody to the same antigen when mature.

Steroids and other agents have been studied not only for their effect on antibody production but also for their effect on tissues. To mention only a few recent papers: Criep[39] found that cortisone had no effect on the antibody levels of rabbits but did diminish the occurrence of lesions and presented serum electrophoretic changes. Spanoudis and his associates[169] were able to inhibit the local Shwartzman reaction by Dicumarol. Arbesman and his co-workers[5] studied the effect of ACTH and cortisone on the pathology of reversed Forsmann anaphylaxis in the guinea pig and found that the lesions characterized by marked hyperemia, capillary hemorrhages, and minimal inflammatory infiltrations in the meninges were ameliorated by a previous injection of ACTH and to a less extent by cortisone.

Schayer, Davis and Smiley[159,160] demonstrated the inhibition by cortisone of the binding of histamine in rat skin both *in vitro* (utilizing C^{-14}) and *in vivo*. Adrenalectomy and prior histamine depletion increased the binding.

Campbell and his co-workers[27] found that cortisone protected against the hemorrhage which occurred as a result of anaphylaxis in transplanted mouse tumors and suggested that this activity of hemorrhage might be due to an immune mechanism.

Humphrey[90,91] found that when circulating neutrophils were reduced to low levels in rabbits by nitrogen mustard or specific antisera, there was a markedly reduced tissue and cellular reaction of the reversed passive Arthus phenomenon, while the reaction was actually increased in animals with reduced platelets by specific antiplatelet antisera.

Rappaport[146] found that the ground substance and the basement membrane of skin from patients with atopic dermatitis stained less intensely than normal skin with the McManus-Hotchkiss method. Atopic skin, after treatment with corticotropin, cortisone and hydrocortisone, showed more deeply stained ground substance and basement membranes, as well as more deeply stained cytoplasm of the fibroblasts and histiocytes. He interpreted the latter changes as due to an arrest, or decrease, in the rate of breakdown of mucoproteins, and possibly also to stimulation of the secretory function of connective tissue cells.

Axelrod and Pruzansky[9] have reviewed the role of vitamins in antibody production and presented data to support the view that antibody response can be inhibited markedly in various vitamin deficiency states.

Other ways of measuring prevention of antigen-antibody reactions in man is the evaluation of various agents for their inhibition of asthmatic symptoms induced by inhalation of aerosolysed antigens such as the past studies of Swineford et al[182] and of Herxheimer[86,88] and Schiller and Lowell.[162] Using animals, Winter and Flataker[201] reported on the quantitative measurement of cough response of passively sensitized guinea pigs exposed to aerosol of specific antigen. They found that the cough is not inhibited by antitussive drugs, codeine and propadrine, but can be inhibited by antiallergic agents such as cortisone and an antihistaminic drug. They found a synergistic effect of cortisone and one antihistaminic drug (pyrilamine).

The literature continues to be filled with the clinical benefits in man derived from corticotropin and adrenal steroids.

Earlier reports[4,21,36,52,64,74,75,115,118,120,147,178] indicated that these compounds exhibited no effect upon the titers of skin-sensitizing or thermostable blocking antibodies, but some diminutive effects upon human skin reactivity, depending upon the concentration and type of solutions used (i.e., inhalants, foods, bacterial antigens, histamine and other compounds). The only reference found in the recent literature is an article by Holti,[89] who demonstrated that ingested cortisone has a slight, but definite diminutive effect upon the immediate skin response to histamine.

Kass and Finland,[106] in their review in 1953, state that inhibition of antibody formation in man usually has not been observed, but the relative degree of hypercorticoidism was probably not so great as in experimental animals and apparently ACTH and cortisone do not interfere with the actual union of antigen and antibody.

Germuth[65] has reviewed the role of adrenocortical steroids in infection, immunity and hypersensitivity and suggests that the failure of cortisone and ACTH to alter antibody levels in man as it does in the lower animal may be due in part to species differences, but points out that dosages ordinarily employed in man are considerably smaller than those used to inhibit antibody formation in experimental animals.

The marked clinical relief of human beings from all types of hypersensitivity cannot, therefore, be accounted for by changes in antigen or antibody of the immediate reacting type. The delayed tuberculin-type of hypersensitivity is frequently, though inconstantly, inhibited in man and experimental animals. The delayed type, however, is characterized by cellular infiltrations.

From what has been accomplished and from what is now known, the problem of selective prevention of antibody formation is still obscure and, as stated by the American Foundation for Allergic Diseases, "Considerable research is necessary in this area," and up this avenue.

HISTAMINE METABOLISM

As pointed out by Rocha e Silva[153] in his recent book "Histamine, Its Role in Anaphylaxis and Allergy," histamine was synonymous with putrefaction up to the early 1920s. It was Sir Henry Dale and his various associates who, since 1910, have presented evidence of the biologic importance of histamine and of the similarity of its effects with those of anaphylaxis. These reports are reviewed by Rocha e Silva.[153] The literature since that time is voluminous with reports of investigation concerning histamine, anaphylatoxin, bradykinin and serotonin. Several pertinent reports have appeared during 1955 and to the time of this presentation in 1956.

Jenden and Tureman[96] described a new technique and apparatus for the study of the action of histamine and various drugs on the isolated lung.

Livingston and Code[117] presented evidence to show that histamine is not conjugated in the liver of dogs and monkeys, although it may be in livers of rats.

Kato and Gozsy[108] reported experiments to show that in an inflammatory process, histamine and leukotaxin appear successively at different and orderly intervals, supporting the view that histamine is present but leukotaxis is formed in tissues.

Back, Feinman and Harrisson[10] found that histamine desensitization slightly decreased the degree of leukocytosis induced by histamine, but did not alter the eosinophil responses.

Benacerraf, Biozzi and Halpern reported[12] that local injections of very small doses of histamine in the skin of guinea pigs or the local application of mild irritants brought about preferentially the appearance of the reaction of passive cutaneous anaphylaxis at the treated sites. They concluded, therefore, that small doses of histamine or other mild inflammatory agents were able to bring about local fixation of circulating antibody.

Studies on the action of histamine liberator compound 48/80 continue. Feinberg and Sternberger,[53] using 48/80 by injection and by inhalation in the guinea pig produced prostration, convulsions and apparent itching of the skin, with hemorrhage in the lungs, but the typical characteristics of histamine shock were not demonstrable. Furthermore, antihistamine failed to prevent the reaction, and they concluded that their results weakened the concept that the major toxic effect of 48/80 is a release of histamine. Kind[109] added further evidence to Feinberg's and Sternberger's concept when he was unable to increase significantly the susceptibility of mice, made highly sensitive to histamine with pertussis vaccine, to 48/80. Mongar[131] compared compound 48/80 with a series of amines in the release of histamine from guinea pig ileum and skin. He found that the amine with a ten carbon chain was more effective than those of six or fourteen carbon atoms, and that this amine was about seven times more

active in releasing histamine than 48/80. On the other hand, when the triple response, rather than direct analysis, was used as a measure of histamine releasing activity, compound 48/80 appeared to be 1,000 times more active. From these results, he questioned whether the wheal test gives a true measure of histamine releasing activity. Bushby and Green[26] reported that polymyxin B and polymyxin E, injected subcutaneously in rats was about as active as 48/80 in releasing skin histamine remote from the injection site, with degranulation of mast cells in the mesentery. They suggested that these observations may be related to the findings that some of the subjective side effects of polymyxin in man are relieved by antihistaminic drugs.

Arunlakshana,[6] upon exposing guinea pig and human lung tissue to two antihistamines (diphenydramine and antazoline), *in vitro*, found release of considerable quantities of histamine. This suggested that this action of antihistamines may be of clinical importance when these compounds are administered at high concentrations, as for instance, when given by aerosol. Mongar[132] inhibited the release of histamine from guinea pig lung tissue sensitized to egg albumin by conducting the experiment in a nitrogen gas environment and concluded that anoxia inhibited release of histamine in anaphylaxis.

Brocklehurst and his associates,[23] studying Arthus and passive cutaneous anaphylaxis in the skin of rats, depleted of its histamine content to 90 per cent, were able to induce reactions of the same intensity as in normal rat skin and concluded that their findings were incompatible with the concept that histamine release is the immediate effect of antigen antibody combination in the skin. Incidentally, reduction of the skin histamine to 10 per cent was accompanied by disappearance of the granules of the skin mast cells.

The recent literature indicates more interest in serotonin (5-hydroxytryptamine) than in histamine per se. Discovery of serotonin perhaps stems back to the early observation (1912) of Janeway and Park,[94] that the serum of clotted blood had vasoconstrictor activity although the plasma of citrated blood did not. The first isolation of serotonin, however, was by Rapport, Green and Page,[148] in 1947, and its synthesis was reported in 1951 by Hamlin and Fisher.[76] During the past year, several reports on serotonin have been made, mostly in association with studies on histamine.

Herxheimer[87] reported that aerosol of serotonin caused a shock syndrome in the guinea pig similar to that caused by anaphylaxis, histamine and acetylcholine. He also found, however, that when guinea pigs, sensitized to egg albumin, were desensitized by repeated exposure to the antigen, their tolerance to serotonin increased and upon resensitization, the tolerance fell to previous values. Furthermore, guinea pigs made tolerant to serotonin became less sensitive to egg albumin, until they lost their tolerance to serotonin.

Humphrey and Jacques[92] reported that the presence of plasma or serum and free calcium ions were essential to release from rabbit platelets of histamine and serotonin by specific antigen. Rabbit plasmas in which antigen antibody reactions had previously occurred did not release histamine from platelets nor show proteolytic activity when tested as little as half an hour later, but such plasmas cause marked increase in capillary permeability when injected into rabbit's skin, irrespective of the presence of platelets. Pretreatment of normal rabbit heparinized plasmas with carbon tetrachloride, agar, glycogen, kaolin and peptone conferred on them the property of releasing histamine from platelets. Trypsin caused rapid release from platelets, but its action was inhibited by some hyperimmune serum. Compound 48/80 and "Thalassine" did not release histamine from platelets. Finally, they concluded that anaphylaxis in the guinea pig is independent of the presence or absence of platelets.

Rowley and Benditt,[157] studying the effects of agents such as ovomucoid, dextran, 48/80 and testis extract, that produce local tissue injury, further supported the hypothesis that agents which damage mast cells, release both histamine and serotonin and that (in the rat) the edema associated with mast cell damage is mediated largely by serotonin.

Pletscher and his co-workers[145] found that reserpine given to rabbits (in doses as low as 0.1 mg per kg) released serotonin in the brain and concluded that their observations supported the view that serotonin has a role in brain function and that the central action of reserpine is mediated through liberation of serotonin.

Costa[38] recently reported that the tranquilizing drugs reserpine, chlorpromazine and Frenquel antagonize serotonin-induced rat uterine contractions, the period of antagonism being longer lasting with reserpine and shortest with Frenquel. Mescaline and LSD caused a facilitation of seratonin activity. These drugs did not affect the sensitivity of the isolated uterus of the spayed rat to acetylcholine or oxytocin. He suggested that if an analogy is possible between the receptors in smooth muscle and the serotonin receptors in the brain, tranquilizing action would seem to be associated with serotonin-inhibiting properties, while the hallucinogenic effects may be related to the facilitation of serotonin.

Several recent reports concern the continued study of the relationship of the mast cells and basophil cells as the source of histamine. Mota and Vugman[135] reported that anaphylactic shock in the guinea pig lung reduced greatly the number of mast cells in the lung and that antihistamines did not prevent mast cells against such damage. Furthermore, 48/80 did not induce any change in the number or morphology of the mast cells. This is in keeping with the findings of Feldberg and Mongar,[54] that the histamine-releasing activity of compound 48/80 is very small when its action is studied on the perfused guinea pig lung.

Wegelius et al[199] reported that antihamster rabbit serum when injected in the cheek pouch of hamsters caused rupture of mast cells, and such damage

was not prevented by an antihistamine (anthisan) locally or intraperitoneally.

Valentine and his associates,[192] studying blood of patients with granulocytic leukemia, reported that the basophil, though small in number, is probably the principal carrier of blood histamine.

Graham and her associates,[73] using a new microchemical method, with dinitrofluorobenzene as a reagent, and spectrophotometric observations described by Lowry and his co-workers,[121] and similar to that of McIntire and his associates,[124,125] reported about half of the histamine of normal blood to be in the basophil, one third in the eosinophil and the remaining one-sixth in all the other blood elements combined. In another report,[72] they found the concentration of histamine in the mast cells of the dog lung and skin to be even greater than that in human blood basophils.

Noah and Brand,[139,140] using the technique described above, by the incubation of antigens of ragweed, timothy, wheat and milk with the blood from human sensitive patients, were able to cause release of histamine into plasma. Those antigens producing the largest skin reactions in any patient also induced the greatest release of histamine. Whereas in some instances clinically significant antigens, particularly food antigens, liberated large amounts of histamine when the skin tests were negative, in others, both skin tests and blood histamine release were negative when there was a good clinical history of sensitivity to an antigen. McIntire[123] pointed out that the chemical assay is superior to bioassay.

Interest has been directed recently to symptoms and signs of a clinical syndrome, associated with carcinoid tumors that occur in the gastrointestinal tract, called Willis argentaffin or Kulchitsky cell carcinomas. When there is metastasis to the liver, symptoms of flushing of the skin, dyspnea, pulmonary stenosis, abdominal pain and diarrhea, edema and ascites occur, and analysis of the blood and urine reveal increased concentrations of serotonin, as described by Isler and Hedinger[93] in 1953. Thorson et al[188] in 1954 reported seven such cases, in which they noted the patients to have "asthmatic breathing" in addition to the symptoms and signs mentioned above. They attributed this syndrome to an increased amount of serotonin released by the carcinoid cells. In 1955, Waldenstrom and Ljungberg,[197,198] reported on the symptoms of carcinoidosis and discussed the chemistry thereof. Sjoerdsma, Weissbach and Udenfriend,[167,168] described a practical test on urine of patients with this syndrome, using the reagents 1-nitrosonaphthol, nitrous acid and ethylene dichloride, that produced a purple color in the presence of the metabolite of serotonin, 5-hydroxyindoleacetic acid (5H1AA), present in the urine of such patients.

A recent book, "Histamine,"[203] in honor of Sir Henry Dale, published under the auspices of the Ciba Foundation symposium, jointly with The Physiological Society and The British Pharmacological Society, contains articles by noted investigators on the various aspects of histamine.

Obviously, this area of histamine metabolism, with the newer knowledge of serotonin, deserves further interest and research. As stated by the American Foundation for Allergic Diseases, "The exact nature of these reactions is unknown and extensive study of the metabolism of histamine may shed new light on the whole subject of allergic disease."

ENZYMES

Since Abderhalden and Pincussohn,[1] in 1909 first introduced the hypothesis that intracellular proteinases were specific, there has been increasing interest, particularly in recent years, in the role of enzymes, such as the protease fibrinolysin or plasmin, their precursors, profibrinolysin or plasminogen and the enzyme inhibitor, antifibrinolysin or antiplasmin, in the antigen-antibody mechanism and histamine release, and particularly since Rocha e Silva[152] liberated histamine from guinea pig lungs by perfusion with trypsin in 1940. Godlowski,[67] in 1953, in his book on the subject, reviewed the enzymatic concept of anaphylaxis and allergy, as well as the role of eosinophils in anaphylactic reactions related to hormonal alterations.

Sevag,[164] in discussing antibodies and hypersensitivity, states that formation of antibody apparently occurs by the formation of a new enzymatic complex between the protein-synthesizing system of the host and antigen. He further states that "cell-bound" reagin may be considered to be cell-bound enzyme protein, which exists in an equilibrium state between normal form and the deformed form as a result of action of sensitizers.

During the past year, several pertinent reports have been made. Burdon and Guthrie,[25] using versene as an antiproteolytic inhibitor, showed that immediate activation of plasminogen to plasmin occurred in rabbit precipitating antisera upon addition of specific antigens, and in the normal rabbit, guinea pig and human sera by addition of anaphylactoid agents, such as peptone. Antigens and peptone activated plasminogen whether they were added to the whole serum or a 1:25 dilution, either before or after heating to 56°C for thirty minutes, and whether they were introduced before or after the protease-inhibitor was removed by versene. They concluded, therefore, that conversion to active enzyme was independent of the presence of natural protease inhibitor and that a complement-like factor is not necessary.

Herberts,[85] studying proteolytic activity in organ extracts after anaphylactic shock, noted an increase in the thiol (—SH) content of the serum, but not so in histamine shock. In shock lung extract, the thiol (—SH) concentration fell during two hours' digestion at 37°C, but this did not occur with normal extract. He concluded that the combination of proteolytic activity and adjustment in the oxidation-reduction balance (—SH groups) during shock implies a severe disturbance of the cellular protein metabolism, which would seem to represent a primary and fundamental factor in the mechanism of anaphylactic shock. The effect of the non-

biologic thiols was assumed to be due to competition with the natural —SH groups of the cell protein and to the reactivation of the inhibitory effect of the antiproteolytic factors of serum.

Ungar and Damgaard,[191] using guinea pig lung and liver, reported that suppression of histamine and heparin release in the anaphylactic reaction can be accomplished by inhibition of proteolysis, suggesting that the latter is the more fundamental reaction.

Nowicki,[141] using urine enzyme from rabbits injected intravenously with gamma globulin, tested the enzyme in combination with the specific gamma globulin in the skin of guinea pigs, rabbits and mice. The enzymatic factor plus antigen gave an inflammatory skin reaction in unsensitized animals, but did not react in the skin of sensitized animals. He concluded that the enzymatic factor was responsible in part for the allergic skin reaction and that the products of early catabolism of the antigen were responsible for the inflammatory reaction in the skin. Further studies by Nowicki[142] showed that the enzymatic factor, produced in rabbits by intravenous immunization with egg albumin, disappeared before the antibodies reached high levels, except during long periods of hyperimmunization, when the enzyme factor appeared together with strong antibody as long as the intravenous antigen was given. The enzymatic factor, however, reappeared many days later and is attributed by Nowicki to the reaction of tissues during immunization and compares this to reaction of tissues of x-irradiation.

As pointed out by the American Foundation for Allergic Diseases, the relationship between enzymes and allergic reactions is a significant area of investigation.

AUTOSENSITIZATION

The field of autosensitization covers many aspects of human disease. The fact that the entire January 1955 issue of the *Annals of the New York Academy of Science* was devoted to the relation of immunology to tissue homotransplantation, with twenty-four articles relative to this subject, indicates the importance of allergy and autosensitization. During 1955 and early 1956, several pertinent reports have appeared in the literature. Cavelti,[29] in discussing autoimmunologic disease, recently reviewed the experimental background and the evidence to support autosensitivity as a probable mechanism in certain blood dyscrasias, rheumatic fever, glomerulonephritis and certain central nervous system diseases. Interest continues to be directed toward the production of encephalomyelitis in the monkey by homologous, as well as heterologous, brains and spinal cord tissues since the first works of Kabat and his associates,[98-101] and Morgan.[133,134] Goldstein and his associates,[68] in studying experimental allergic encephalomyelitis, found that the chloroform-soluble portion of brain contained the most encephalitogenic activity.

Waksman and Adams[196] reported on the differences in symptomatology and spinal fluid findings of experimental allergic encephalomyelitis and ex-

perimental allergic neuritis. Using homologous rabbit sciatic nerve or spinal ganglia, lesions were produced in the roots, ganglia and peripheral nerves, but not in the central nervous system, nor in the meninges.

Mountain[137] was able to produce a rabbit antiserum to HeLa cells which had the capacity to agglutinate and lyse HeLa cells in culture. Makari and Huck[122] reported being able to sensitize guinea pigs to antigen in carcinomatous tissues incorporated with Freund's adjuvants. Such sensitized uterine horns could respond specifically to carcinomatous antigens present in the sera of carcinomatous patients.

Freund, Thompson and Lipton,[60] were able to produce aspermatogenesis, anaphylaxis, and cutaneous sensitization in guinea pigs by injection of a purified, homologous testicular extracts combined with adjuvants.

Witebsky, Rose and Shulman[154,166,202] were able to study the antigenicity and cross-reactivity of thyroid extracts derived from homologous and heterologous species, using precipitin and complement fixation techniques to measure activity.

Boake and Muir[18] were unable to produce auto-antibodies or arthritis in rabbits by injecting a vaccine consisting of rabbit chondroitin sulfate and hemolytic streptococci. Pearson,[143] however, was able to produce generalized or focal arthritis, synovitis, periostitis and tendonitis in rats by intracutaneous injections of homologous macerated striated muscle of rat incorporated in a Freund-type adjuvant.

Mellors, Siegal, Pressman[130] adapted Coons' and Kaplan's technique to demonstrate the histologic components of tissue and the sites of *in vivo* localization of antibodies. Among interesting findings were that rabbit antibodies against kidney and lung of the rat localize in the renal glomeruli when injected into the rat, achieving maximum concentration in the glomerular basement membranes.

In a different type of study of renal disease, Spar and associates[170] used a radioactive-labeled extract of rabbit kidney derived from rabbits which had been immunized against rat kidney. This antigen (anti-rat rabbit kidney) was injected into rabbits and rats to test for preferential localization. Similar experiments were done with normal rabbit kidneys. Preparations from both sources showed preferential kidney localization in both rats and rabbits persisting for days.

Gear[63] hypothesizes that many important diseases in man may result from the action of autoantibodies developed against tissues made autoantigenic by some alteration to the tissue cells. Such an alteration may be caused by infections, drugs, and other chemicals and by physical agents, including x-rays, heat and cold.

The experiments of Wagner, Seba and Hruskova[195] demonstrated the presence of tissue autoantibodies in the blood serum of patients with certain skin diseases. The authors used various organs from persons who had recently died. Autoantibodies were found in three patients with lupus erythematosus, two with pemphigus and one with impetigo herpetiformis

Hebra. The titers of antibodies were for the greatest part in correlation with clinical damage of organs.

It has been known for many years that homologous grafts of skin do not survive, as originally emphasized by Medawar[127] in 1944. It has been pointed out by Cooke[33] that the failure of homografts to "take" may well be due to allergy and that evidence to date suggests the reaction to be of the immediate rather than the delayed type of allergy, but whether the allergy is an effect or a cause remains obscure.

Sulzberger[183] suggested, as did Cooke, that further immunologic studies in man, employing human epithelium and extracts of human dander, might possibly succeed in illuminating many problems related to human reactions to skin homotransplants.

Hardin and Werder[78] reported that multiple subcutaneous injections of skin extracts into mice, starting about the time of transplantation, resulted in permanent viability in the majority of the homologous skin transplants. Billingham and Medawar[17] had been unsuccessful in a previous attempt (1953) to accomplish this in rabbits, as were Kaliss and Spain.[105] Hardin and Werder[78] attributed their success to multiple injections of the homologous antigens, since single injections met with negative results in their hands.

Toolan[189] reported the successful transplant of human sarcoma to the cheek pouch of the hamster by administering cortisone to the recipient hamsters. The animals furthermore tolerated a second transplant of the same antigen. This is in contrast to second transplants of homologous normal skin grafts which "break down" more rapidly than the first.

Billingham and his co-workers[16] reported that tolerance to skin homografts may be artificially induced by exposing rabbits, mice and chickens to living tissue antigens in the period of development before the faculty of immunologic response has come into being. The earlier the embryo was inoculated, the greater should be the success, according to these authors.

Gorer[69] reported red and white cell agglutinin production in mice following skin homografts and presented evidence that skin homografts in man stimulate antibodies reacting with human red cells. He further hypothesized that clinical use of skin homografts may incur risk in subsequent blood transfusions and states that women below the menopausal age should receive homografts only if such grafts are essential to save life.

Stark et al[174] reported that two antihistamines (Benadryl® and Histadyl®), and sodium salicylate, given to recipient mice, and x-irradiation of the recipient site, caused the homotransplant survival to be prolonged over that of controls, but no peripheral ingrowth of capillaries, such as seen in autografts was observed.

Kaliss and Kandutsch[104] found that antisera to mouse tissues, produced in rabbits or mice, induced acceptance of an otherwise incompatible tumor homograft in mice, when injected into the host prior to grafting of the tumor. The activity of the antiserum was associated with the globulin

and was most concentrated in the gamma globulin fraction. The activity was not impaired by treatment with sodium periodate or by heating to 56°C, was slightly impaired at 70°C, and completely destroyed at 100°C.

Bonfiglio et al[19] administered injections of extract of rabbit ulnar bone, and produced complement-fixing antibodies and marked decrease in inflammatory response to bone grafting in rabbits when compared with control animals, who showed no antibodies and marked tissue reaction following bone grafts.

As stated by the American Foundation for Allergic Diseases, "the ramifications of this area of research are endless and need investigation."

COLLAGEN DISEASE

The importance of this avenue of research in the field of hypersensitivity has been evident for several years. Much of the clinical and experimental aspects of all phases of this category has been summarized most recently by Talbott and Ferrandis.[184] Several reports on this subject have been made since January, 1955.

Rich[150] induced glomerulonephritis in experimental rabbits by a single intravenous injection of 10 ml horse serum in fifty-three (61 per cent) of eighty-seven animals. The appearance of the lesions appeared fourteen to eighteen days after injection.

Rothbard and Watson[156] were able to induce reversed anaphylactic shock in rats by the intravenous injection of serum containing complement-fixing antibodies, obtained by immunization of rabbits with purified preparations of rat-tail collagen. The anaphylactic reaction was specific for the antigen and antibodies of rat collagen.

Booth and associates[20] found that the staining and histochemical characteristics of the fibrinoid material encountered in the kidney of rabbit subjected to the Shwartzman reaction were similar to those of necrotic arterioles observed in malignant hypertension.

Stavitsky and his associates,[175] also studying renal disease, reported that of seventy-four rats, following injection of duck anti-rat kidney serum, from 10 to 20 per cent of two series of rats developed renal disease without a latent period. There was no correlation between the time of appearance of complement-fixing antibodies and onset of renal disease, although there was a relationship between the severity of the disease and the length of the latent period.

Using a microfluorescence method for demonstrating the histologic sites of localization of antibodies *in vivo*, Mellors and his associates[129] examined rabbits who had received one or more intravenous injections of purified proteins of bovine gamma globulin. Of fifteen rabbits, twelve developed glomerulonephritis, eight myocarditis, three endocarditis, five interstitial pneumonia, four allergic angiitis, fifteen lymphoid hyperplasia of the spleen and two allergic granulomas of the spleen. The pathologic characteristics of each lesion relative to localization of antibody was described.

Wood and White,[204] also using fluorescein-labeled antibody, studied experimental glomerulonephritis produced in mice by subcutaneous injection of heat-killed *Proteus mirabilis*. The authors suggest that the localization of bacterial antigen in glomerular cells may be casually related to the production of nephritis and that this localization site is related to the type of glomerulonephritis produced in mice which resembled Ellis Type I nephritis in man.

Kopeloff and Kopeloff[110] produced a delayed allergic inflammatory reaction in the knee joint of the guinea pig by a single injection of rabbit serum into the synovial cavity, when accompanied by simultaneous systemic sensitization with rabbit serum in Freund's adjuvants. A delayed allergic inflammatory reaction was elicited in the hind foot in which rabbit serum had been injected one to two weeks prior to the subcutaneous nuchal injection of a rabbit serum adjuvant emulsion.

Perry,[144] in studying the possible restorative effect of follicular stimulating hormone-damaged testes of rats, found that, instead of restoration to normal testicular activity, there was degeneration of tubules and periarteritis of interstitial arterioles. Autopsies eight to twelve months after treatment showed that periarteritis nodosa was present in the intestinal, mesenteric, pancreatic, splenic and other small arteries, but not in the pulmonary arterioles. Small vessels of kidneys, adrenal and pituitary were also involved. Other pathologic changes were noted.

Salgado and Selye[158] performed experiments, among others, to show that STH (somatotrophic) hormone has the ability to sensitize the body to the toxic action of such steroids which can induce nephrosclerosis, hypertension and cardiovascular lesions.

Thomas,[187] in discussing the mechanism involved in the vascular lesions produced by endotoxins, reports work in which an intradermal injection of liquoid (sodium polyethanol sulfonate, a synthetic acidic polymer), accompanied by an intravenous injection of endotoxin, regularly produced cutaneous lesions of periarteritis nodosa, with deposits of fibrinoid material in and around the walls of all small and medium-sized arteries. Furthermore, when this same substance, liquoid, is added to whole human blood, there is produced, after fifty minutes incubation, intracytoplasmic bodies in the polymorphonuclear leukocytes which are similar to those seen in LE cells.

Kass and Finland[106] and Germuth[65] discussed the anti-inflammatory effect of cortisone and ACTH in the human being and the experimental animal. Nearly all of the so-called collagen diseases usually respond, to a certain degree, to those hormones. Kass and Finland[106] state "that it is not clear why the passive Arthus phenomenon should be unaffected by the action of adrenocortical hormones whereas the Shwartzman phenomenon, which is histologically similar, is inhibited. Nor is it clear why, in the Shwartzman phenomenon, the effect of the preparatory dose of toxin should induce an unusually severe response in the cortisone-treated animal,

whereas the effects of the second or challenge dose of toxin may be inhibited."

Eisen and Tabachnick[49] have reviewed the subject of protein metabolism, and point out that abnormalities of the plasma protein patterns in collagen diseases are generally of a nonspecific character and that such patterns, although often useful in establishing diagnosis, rarely can be regarded as pathognomonic.

As stated by the American Foundation for Allergic Diseases, "A more thorough study of the possible antigen-antibody reactions involved here may be very rewarding."

COMMENT

Whereas investigation in the six areas herein reviewed is most important to the better understanding of allergic disease, there are other areas of research that are pertinent to allergy, including pulmonary function and aerosol studies; drug allergy *per se;* bacterial allergy *per se;* hormones other than adrenal steroids; preparations and fractionation of antigens, particularly for use as allergenic extracts in clinical as well as investigational allergy; and the clinical syndromes of allergic dermatoses, hay fever, asthma, gastroenteritis and others. The practitioner may have a tendency to disregard and consider lower animal experimentation as material not pertaining to his interest, but he should respect it, keep abreast of it, and realize that such research serves to form a link in the chain that will lead to better understanding of allergy and, in turn, more accurate diagnosis and more effective treatment of patients with allergic diseases.

SUMMARY

The American Foundation for Allergic Diseases has announced recently its program to support six areas of research in allergy pertaining to (1) ways in which cells of the body are affected by antigen-antibody reactions, (2) ways of preventing antibody formation, (3) histamine metabolism, (4) enzymes, (5) autosensitization, and (6) collagen diseases. Selected pertinent reports of research in each of the six aforementioned areas appearing in the medical literature of 1955 and early 1956 have been reviewed.

The new National Institute of Allergy and Infectious Diseases should make new and additional fundamental research in allergy possible.

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Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

STEROID HORMONES AND THE PANCREAS

In sixteen of fifty-four patients given steroid hormones for periods varying from several days to several years two investigators of the Yale University School of Medicine* discovered post-mortem evidence of acute pancreatitis or peri-pancreatic fat necrosis or both. In only two of a control group of comparable age and illness were similar pathological changes noted. Considered as equally responsible for the lesions were all five commonly-used steroid preparations namely, cortisone, hydrocortisone, prednisone, prednisolone, and corticotrophic hormone.

During life, clinical evidence of the changes in the pancrease was apparent in only six of the patients. Of the others, six were mildly affected and seven more moderately so. The effects were severe in three. Of those with mild or moderate lesions there was no premortem clinical record of any degree of pancreatitis and no obvious evidence of fat embolism. Alteration of pancreatic secretion and release of pancreatic enzymes producing obstructive acinar changes are advanced as the most likely hypotheses.

We now have one more cogent reason for continuing with the classic methods of diagnosis and treatment, that is, the careful detailed history, the meticulous studies, the elimination of the environmental allergens, the injection treatment of seasonal allergens and the rehabilitation, physically and psychologically, of the allergic patient.

The steroid hormones, (however improved!), should be used in minimal doses in short courses and only when the indications are absolute. They are not and never have been substitutes for a well trained conscientious allergist.

*Caron, F. A., and Liebow, A. A.: New England J. Med., 257:690, 1957.

SOUTHWEST ALLERGY FORUM

Announcement is being made of the annual meeting of the Southwest Allergy Forum which will be held in Houston, Texas, at the Shamrock-Hilton Hotel, April 26, 27 and 28, 1959. Address inquiries to Richard L. Etter, M.D., President, Hermann Professional Building, Suite 156, Houston 25, Texas.

In Memoriam

MAX HARTEN, M.D.

Max Harten, of Brooklyn and Great Neck, was President-elect of the Brooklyn Allergy Section of the Kings County Medical Society at the time of his death on May 24, 1957. Doctor Harten was an associate attending physician at Kings County Hospital and at North Shore Hospital, Manhasset. In 1934, he was graduated from Long Island College of Medicine and served his internship at the Brooklyn Jewish Hospital. Dr. Harten was a Diplomate of the American Board of Internal Medicine and was elected to Fellowship in The American College of Allergists, March, 1957.

HUGH ALVA KUHN, M.D.

On April 17, 1958, Dr. Hugh Kuhn, for thirty-five years a physician, a leader in his profession, a citizen and a friend to many, died in Chicago.

Dr. Kuhn was born in Lore City, Ohio, November 16, 1895. He graduated from Muskingum College, receiving the doctor of medicine degree in 1919 from the University of Cincinnati. He did postgraduate work at the University of Bordeaux, the New York Eye and Ear Hospital, and the University of Vienna, as well as at Bellevue Medical College. He was a Diplomate of the American Board of Ophthalmology and of the American Board of Otolaryngology. He was a Fellow of The American College of Allergists and served as secretary of the Otolaryngology Section of the American Medical Association from 1953-1956.

At the time of his death, Doctor Kuhn was head of the Kuhn Clinic of Hammond, Indiana. His wife, Dr. Hedie Kuhn, and his son, Dr. Arthur Kuhn, will continue the clinic. His other son, Dr. Robert Kuhn, practices in Columbus, Ohio.

HENRY LEWIS TURKEL, M.D.

Henry Lewis Turkel, of the Bronx and New York City, died on October 6, 1957, at the age of sixty. He was graduated in 1923 from Albany Medical College and interned at Lying-In Hospital. Doctor Turkel was an adjunct professor in allergy at New York Polyclinic Medical School and worked in the Allergy Departments of the Polyclinic Hospital and Lenox Hill Hospital. Doctor Turkel was elected a Fellow of The American College of Allergists January 23, 1945.

ROCKY MOUNTAIN ALLERGY SOCIETY

Officers elected to serve the Rocky Mountain Allergy Society during 1958 are:

Harold S. Tuft, M.D.....President
John W. Bradley, M.D.....Vice President
W. Grayburn Davis, M.D.....Secretary-Treasurer

Papers of Interest

Beutler, E.: The glutathione instability of drug-sensitive red cells. A new method for the *in vitro* detection of drug sensitivity. J. Lab. & Clin. Med., 49:84, 1957.
Blood samples are incubated with acetylphenylhydrazine. The reduced glutathione level is measured before and after incubation.

Leyton, N.: The modern treatment of migraine. Lancet 77:24, 1957.
Injections of chorionic gonadotrophin (pregnyl and Antuitrin-S), prostigmin desensitization, carbachol, bellergal are advocated. Histamine acid phosphate, prostigmin desensitization, chorionic gonadotrophin and heavy-dosage of vitamin B_2 are used for treatment of severe migraine.

Cohen, A. S.: Acute Schönlein-Henoch purpura treated with prednisolone. Brit. M. J., 1:143, 1957.
A patient who did not respond to cortisone did respond to large doses of prednisolone.

Overmiller, W. C., and Stover, W. H.: Perforated gastric ulcer complicating Prednisone therapy. California Med., 86:52, 1957.
Perforation of a gastric ulcer occurred in a patient given long-term treatment with prednisone for rheumatoid arthritis. Its presence was not suspected.

Chapman, D. G.; Chatten, L. G.; and Campbell, J. A.: Physiological availability of drugs in tablets. Cand. M. J., 76:102, 1957.
Eleven brands of tablets were evaluated for disintegrations and a great discrepancy was noted by the Food and Drug tests as compared to the manufacturers' claims.

Lin, F. K. and Coriell, L. L.: The effect of combined antibiotics on the *in vitro* emergence of staphylococci resistant to novobiocin. Antibiotic Med., 4:35, 1957.
Combined antibiotic agent treatment is ineffective.

Harwood, C. T., and Mason, J. W.: Acute effects of tranquilizing drugs on the anterior pituitary-ACTH mechanism. Endocrinology, 60:239, 1957.
In monkeys, reserpine and chlorpromazine both stimulate the anterior pituitary-ACTH system and cause increased plasma 17-hydroxycorticosteroid concentration.

Friedman, A. P.: Use of tranquilizers in the treatment of headache. Am. Pract. & Digest Treat., 8:94, 1957.
Meprobamate may reduce emotional tension associated with headache. Reserpine is helpful in reducing the frequency of the headaches of hypertension.

Maganzini, H. C.: Anaphylactoid reaction to penicillins V and G administered orally: report of two cases and brief review of the subject. New England J. Med., 256:52, 1957.
Physicians should be able to cope with anaphylactoid reactions. Reactions to penicillin are being reported more frequently. Physicians must be able to cope with the immediate anaphylactic response.

Carter, C. H., and Maley, M. C.: The clinical value of toclase in suppressing the cough reflex. Am. J. M. Sc., 233:77, 1957.
The cough reflex was reduced or suppressed in 91 per cent of 557 patients. No side effects were noted.

Good, R. A.; Vernier, R. L.; and Smith, R. T.: Serious untoward reactions to therapy with cortisone and adrenocorticotropin in pediatric practice. J. Pediat., 19:95, 1957.
A review with case records supported by ninety-five references.

Adams, J. M.: Acute respiratory diseases, etiologic, diagnostic and therapeutic considerations. Pediatrics, 19:129, 1957.
A review. Routine forcing of fluids is condemned.

Delaunois, A. L.; Dautreband, L.; and Heymans, C.: Method for administering micromicellar aerosols to guinea-pig isolated lungs. Arch. internat. de pharmacodyn. et de thérap., 108:238, 1956.
How to measure changes of lungs following use of aerosols which reach and affect the alveoli.

Mauer, A. M.; DeVauz, W.; and Lahey, M. E.: Neonatal and maternal thrombocytopenic purpura due to quinine. Pediatrics, 19:84, 1957.
The presence in a mother and a newborn infant was confirmed by finding quinine-platelet antibodies in the plasmas. Does this explain toxic sensitivity in other neonatal cases?

PAPERS OF INTEREST

Sous, H., and Muckter, H.: An antihistamine-penicillin drug (megacillin) with protracted depot effect. Arzneimittel-Forsch., 6:718, 1956.
Describes higher blood levels than those measured with equivalent preparation of procaine-penicillin.

Van Horne, R. G.; Saslaw, S.; Anderson, G. R.; Flatley, J. F.; and Carr, R. D.: An intrafamilial epidemic of pharyngoconjunctival fever. Arch. Int. Med., 99:70, 1957.
APC virus was isolated from three of seven patients with acute illness. A rise in serologic titer was measured in four in whom the presence of pharyngoconjunctival fever was proven.

Gillen, A.; Timm, E.; and Pucheu, A.: Studies on the antigens of adenoviruses. Canad. J. Pub. Health, 48:25, 1957.
The "soluble" antigen is relatively heat-labile, and destroyed, at pH-1, in thirty minutes.

Ruesch, J.: The trouble with psychiatric research. Arch. Neurol. & Psychiat., 77:93, 1957.
Review supported with fifty-six references.

Am. Rheumatism Association: Rheumatism and arthritis. Review of American and English literature of recent years. The eleventh rheumatism review.
Discusses collagen diseases and a number of other disorders with approximately 2,500 references.

Rivera, J. V.; Rodriguez, H. F.; and Perez-Santiago, E.: Thrombocytopenic Purpura due to Fuadin. Am. J. Trop. Med., 5:863-868, 1956.
A case of thrombocytopenic purpura after Fuadin, which could be reproduced by administration of the drug. Thrombocytopenia could also be experimentally produced in a person who had received Fuadin followed by injection of 250 ml plasma of the patient.

Parrot, J.-L., and Laborde, C.: Studies on the allergic terrain: Trial of treatment with normal human serum. (In French). Presse méd., 64:1765-1768, 1956.
The authors describe "allergic hyperhistaminemia" as a basic disorder of patients suffering from asthma, urticaria, eczema, migraine, and a number of other disorders in their "allergic" forms.

Traut, E. F., and Passarelli, E. W.: Placebo in the treatment of rheumatoid arthritis and other rheumatic conditions. Ann. Rheumat. Dis., 16:18-21 (March) 1957.
The effect of placebo tablets on a total of eighty-eight patients studied showed the number of patients who improved after placebo treatment is about the same as that of those improving after other therapy, as shown in other reports.

Copello, F., and Cajati, M.: Prednisone and prednisolone in treatment of eczema in nurselings and young children. Minerva pediat., p. 250-257 (March 3) 1957.
Prednisone was used in nineteen infants of whom seventeen were eczematous and two asthmatic, and prednisolone in sixteen more, of whom fifteen were eczematous and one asthmatic. Prednisolone appeared to be the quicker acting drug.

Strauss, John S., and Kligman, Albert M.: Atopic dermatitis; a discussion of its pathogenesis. New England J. Med., 256:1002-1003 (May) 1957.
When the eight subjects were given rhus dermatitis, and then crab or pollen extracts, to which they responded with skin tests (but no eczema), were applied or injected, exacerbations occurred prolonging healing time.

Douglas, A. C.; Somner, A. R.; Marks, B. L., and Grant, I. W. B.: Effect of antibiotics on purulent sputum in chronic bronchitis and bronchiectasis. Lancet, 2:214 (Aug. 3) 1957.
Of 131 patients those who did not respond to penicillin, 78 per cent were favorably influenced by chloramphenicol and 39 per cent by oxytetracycline.

Williams, G. T., and Welch, G. E.: A controlled study of prednisone, aspirin and a placebo in degenerative joint disease. South. M. J., 50:1063 (Aug.) 1957.
Another of interest to investigators in the field of drug therapy is the fact that, although prednisone was 78 per cent effective, acetylsalicylic acid gave equally good results in 65 per cent and the placebo 40 per cent of the patients.

Prolonged antibiotic treatment of severe bronchiectasis. A report by a subcommittee of the antibiotics clinical trials (non-tuberculous) committee of the medical research council. Brit. M. J., 2:255 (Aug. 3), 1957.
Of 122 patients with bronchiectasis treated at random with lactose, penicillin or oxytetracycline, the third gave best results.

PAPERS OF INTEREST

Good, R. A.; Vernier, R. L., and Smith, R. T.: Severe reactions to cortisone and ACTH. Modern Med. 25:123-125 (Apr. 15) 1957.
Discuss intercurrent infection, central nervous disorders, gastrointestinal reactions, fluid and electrolyte imbalance, diabetes mellitus, osteoporosis and pathologic fracture, adrenal cortical deficiency, and therapeutic precautions.

Meneely, G. R.: Pulmonary function testing. Dis. Chest, 31:125 (Feb.) 1957.
Defines objectives and means of estimating all aspects of pulmonary functions.

Antibiotics—a panel discussion. Am. Coll. Surgeons, 1956 meeting. Harper Hosp. Bull., 15:82 (Mar.-Apr.) 1957.
Chloromycetin is given top honors.

Palmer, K. N. V.: The effect of an aerosol detergent in chronic bronchitis. Lancet, 1:611 (March 23) 1957.
Both an aerosol solution containing a detergent and sodium bicarbonate, and a control solution were valuable in thinning mucus in patients with chronic bronchitis.

Becker, S. W., and Mounce, S. H.: Dermatoses in patients receiving chemotherapy for systemic tuberculosis. AMA Arch. Dermat. & Syph., 75:333 (March) 1957.
Eighty-seven of 239 patients given streptomycin presented skin reactions suggestive of neurodermatitis.

Platzer, R. E.; Springs, C., and Glasser, G. L.: Agranulocytosis due to chlorpromazine. New York J. Med., 57:1424 (Apr. 15) 1957.
Two case reports.

Challenge for antibiotics. Chem. Eng. News, 35:22 (Apr. 22) 1957. (News Note).
New synthetic hexahydropyrimidines are antimicrobial for both Gram-positive and Gram-negative bacteria and for fungi.

Nolen, W. A., and Dille, D. E.: Use and abuse of antibiotics in a small community. New England J. Med., 257:33 (July 4) 1957.
Over a five-year period, 763 patients suffering from 2,936 separate illnesses were injected with antibiotic agents, not indicated in 52.5 per cent of the occasions they were used.

Cole, J. G.; Cole, H. G.; and Janoff, L. A.: A toxic ocular manifestation of chloramphenicol therapy. Report of a case of optic neuritis. Am. J. Ophth., 44:18 (July) 1957.
With cessation of chloramphenicol and administration and initiation of vitamin B_{12}, diamox and thiamine chloride treatment, vision returned to normal. Frequent examination of eyes during long-term administration of chloramphenicol is suggested.

Samuels, Arthur S.: Acute chlorpromazine poisoning. Am. J. Psychiat., 113:746-748, 1957.
The patient demonstrated central nervous system depression and convulsions. The treatment consisted of intravenous instillation of dextrose, the administration of a broad spectrum antibiotic to prevent infection and the use of norepinephrine to correct hypotension.

Venning, G. R.: Aplastic anaemia due to phenylbutazone. Brit. Med. J., 2:146 (July 20) 1957.
The first recorded case of aplastic anaemia following phenylbutazone had received treatment with gold salts. This is the second reported case.

Benians, R. C., and Hunter, J.: Megaloblastic anaemia occurring during treatment of epilepsy with phenytoin sodium primidone and phenobarbitone. J. Mental Sci., 103:606 (July) 1957.
One of the epileptic patients died from megaloblastic anaemia during treatment with phenytoin sodium, primidone and phenobarbitone. Two others recovered following administration of folic acid orally.

Council on drugs report. Potential hazards of meprobamate. J.A.M.A., 164:1332 (July 20) 1957.
Meprobamate is habit forming and withdrawal symptoms, convulsions and sleepiness, may occur. Acute intoxication is a possibility. Sensitivity is shown as dermatitis.

Fudenberg, Hugh and Allen, Fred H., Jr.: Transfusion reactions in the absence of demonstrable incompatibility. New J. Med., 256:25 (June 20) 1957.
In two cases of severe hemolytic transfusion reaction, specific antibodies appeared in the patient's serum. Their absence was confirmed in the pretransfusion serum.

Richter, Tor; West, John R., and Fishman, Alfred P.: New England J. Med., 256:25 (June 20) 1957.
Case report of a patient with alveolar hypoventilation secondary to a damaged respiratory center, but with normal lungs and with normally functioning chest bellows.

BOOK REVIEWS

PRACTICAL ALLERGY. M. Coleman Harris, M.D., and Norman Shure, M.D. 471 pages, including bibliography and index. Philadelphia: F. A. Davis Company, 1957. Price $7.50.

This new textbook is distinguished by a number of special features. Among others is the printing of a long-overdue Pollen Table, wherein are listed, according to cities, the important allergenic plants of the United States, indicating their relative importance based upon the amount of pollen shed, their abundance, proximity to centers of habitation and clinical reactivity in patients. A European Pollen Table should prove useful to physicians wanting to advise tourist-minded patients what plants may be pollinating while they are in Europe. The photography of fifteen wind pollinating plants is excellent.

There is a short chapter on the Emotional Factor in Allergic Disease. It stresses that, in addition to the customary history of allergic disorders, a psychological history is important. The authors feel that physicians should realistically evaluate the prognosis in each case of allergic disease, and should not delay in referring disturbed patients to qualified psychiatrists. A new-type History Form, with marginal suggestions, is offered for those who practice occasional allergy.

In the chapter on Office Allergy Technic, cleaning and proper sterilization of needles and syringes, diluting of extracts, filling of allergy vials and preparing antigens are discussed.

A complete chapter on Drug Allergy is included. The final chapter, Materia Medica, lists the drugs commonly used in the treatment of allergic diseases. Both the pharmacological names and manufacturers' trade names are given along with the doses commonly prescribed.

This text, which was originally intended for the general practitioner, and the ear, nose and throat specialist, is good reading for physicians currently practicing "part-time allergy."

DERMATOLOGIC FORMULARY. New York Skin and Cancer Unit. Second edition. Edited by Frances Pascher, M.D. 172 pages. Price $4.00. New York: Paul B. Hoeber, Inc., 1957.

The Dermatologic Formulary is no mere basic list of prescriptions for clinic use. It is broad enough in scope to allow individualization of therapy and specific enough in its direction to be extremely useful to anyone who must treat a skin disease.

This second edition has been expanded to reflect the large place that corticosteroids have come to occupy in dermatology, both as systemic therapy and for topical use alone, and in combination with other medicaments. Many other new medications have been added, and the deletion of a number of less useful (or perhaps simply less used) items indicates the constantly changing nature of dermatologic therapy.

The action of each drug or formulation is briefly noted, and the indications, directions for use, side effects and contra-indications are clearly stated.

Topical remedies, systemic medication, and materials for office or clinic use are included in this book. There are also general direction sheets for the use of dermatologic modalities, and for the management of such conditions as acne, pyoderma and ringworm. The proper control of patients on long-term corticosteroid therapy is well summarized.

This small volume is a valuable addition to the medical library.